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PERIARTERITIS NODOSA

REPORT OF A CASE

REGINALD FITZ, M.D.

HARRY PARKS, M.D.

AND

CHARLES F. BRANCH, M.D.

BOSTON

Periarteritis nodosa is a baffling disease. Many clinicians agree with Kussmaul and Maier [1] that its prognosis too often is obvious long before its diagnosis can be established.

A voluminous literature describing periarteritis nodosa has accumulated since Kussmaul's day; so bulky a literature, in fact, that to report another case seems scarcely excusable. We have had occasion, however, to study a patient with periarteritis nodosa during twenty months of almost continuous hospitalization and (through many friends who saw her) to develop a record of her case which we believe gives a fairly complete account of the evolution of the disorder in this particular instance from early in its course until the end. The entire affair was peculiar enough to be interesting. Some of the observations made do not appear to have been reported in other cases on record. Finally, any light that can be shed on periarteritis nodosa may prove helpful to future patients.

REPORT OF CASE

M. K., an attendant nurse, was 37 years old at the time of her death. She felt perfectly well until September 1928, eleven years before her illness terminated. After riding in the wind one day she noted a paralysis of the right facial nerve. She could not remember how incapacitating this was; later, as she recalled the episode, she remembered the development of a sensation of quivering and stiffness of the muscles of her face without any particular weakness of the muscles of mastication or expression and a continued sensation as though every movement of her face were under a skin which had been freshly sunburned.

From the Robert Dawson Evans Memorial for Clinical Research and Preventive Medicine.

1. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. **1**:484-518 (Feb.) 1866.

In 1929 this sensation spread to involve the other side of her face. Persons, however, would laugh at her when she said she had "facial paralysis," for the expression of her face seemed natural, and there was no obvious muscular weakness or atrophy.

In 1931 she began to notice what she termed a quivering feeling in her legs at night when she lay down. She could not find a comfortable position for her legs. There was no actual pain but a jerkiness of the small muscle bundles.

In the fall of 1934 she noticed that her legs were quickly fatigued and began to ache when she climbed stairs and that her feet felt numb and unreal. Presently her legs began actually to hurt when she used them, to swell and to show red spots when she stood up much. Finally, for no reason that she knew, she began to have bouts of diarrhea. These were painless and consisted in the passage of about three normal-looking stools each day.

There was no tuberculosis in the family. She had never been seriously ill. After graduating from high school she worked as a clerk in a factory office. She had a course of training in the Emerson Hospital in Concord, Mass., and since 1933 had been doing private nursing almost constantly.

It may be significant that in 1926 and again in 1929 she had an attack of tonsillitis. Both attacks were severe; with each there were fever, malaise, prostration and about a week's illness in bed followed by a week's convalescence before she felt like going back to work. There was no more evident relation than this, however, between the tonsillitis, the "facial paralysis" and the muscular weakness and soreness of which she complained.

Three other points are worthy of comment. For several years she had noticed that her eyes failed to accommodate promptly. If she glanced at a near object after looking at a distant object there would be a few seconds of blurring until accommodation occurred. This difficulty was not corrected by glasses. It bothered her because she herself had noticed the development of this peculiarity and she wondered what it meant.

She had had good teeth, but since 1933 they had been too soft; her dentist told her that something was wrong with her metabolism and that this made her teeth unduly susceptible to decay.

Finally, since 1933, or for about a year before she came under medical supervision, she had been plagued by an irritating, tickling type of chronic cough. It reminded her of whooping cough without the whoop; and cough as she would, she could raise nothing. She had painted her throat, had tried various "cough medicines," all without benefit, and on the whole had found nothing helpful.

It was with a story as indefinite as this that M. K. consulted Dr. Richard Stetson of Boston in November 1934. She was worried about the way she felt, about her cough and about the manner in which her legs misbehaved; she wondered how serious an illness she had and whether it would become increasingly incapacitating.

Physical examination at that time revealed no abnormality except in the nervous system. The pupils were irregular and fixed to light. There was lateral nystagmus. The tongue deviated to the left. The arm jerks were exaggerated, the right being livelier than the left. The abdominal reflexes were absent, as were the ankle and knee jerks. There was no Babinski sign. Sensations of position and vibration in the feet were poor, and there was a definitely positive Romberg sign. There was hypesthesia of the stocking type over the lower parts of both legs. Disturbances in sensation were much more notable than were motor disturbances.

Thereafter the disease followed a zigzag course. The patient was studied from time to time in various hospitals, and it is interesting to realize how varied were the opinions offered as to diagnosis (table 1). These reflect fairly well what happened to the patient subjectively.

At first the clinical picture was that of an ill defined, diffuse disease of the nervous system, not following any definite rule and seemingly better classified as possible multiple sclerosis than anything else. Presently, however, there developed a beefy red tongue; with this there occurred intermittent attacks of diarrhea, the conditions being superimposed on what looked more and more like peripheral neuritis. Thus the question of avitaminosis and nontropical sprue arose. In 1934 bouts of fever began to occur, and at times a transitory cutaneous rash would appear. The cutaneous lesions were variously described as erythema, as urticarial wheals, as papules which made one think of insect bites or even as frankly purpuric spots. In the fall of 1936 the patient was observed at the Peter Bent

TABLE 1.—*Diagnoses Suggested at Various Hospitals in the Case of a Patient with Early Periarteritis Nodosa*

Hospital 1 November 1934	Hospital 2 March 1935	Hospital 3 June 1935	Hospital 4 July 1935	Hospital 5 February 1936	Hospital 6 November 1936
? Multiple sclerosis	? Multiple sclerosis	? Multiple sclerosis	Multiple neuritis (cause undetermined)	? Nontropical sprue	Erythromelalgia
	? Nontropical sprue		?? Syphilis of the central nervous system	? Avitaminosis	? Raynaud's disease
	? Avitaminosis				? Thromboangiitis obliterans
					? Multiple neuritis (cause undetermined)
			Treatment		
	Antisprue diet; liver extract; high vitamin diet	Fever therapy	Antisyphilitic therapy	Antisprue diet; liver extract; high vitamin diet; tonsillectomy	High caloric diet; high vitamin diet

Brigham Hospital. Dr. H. A. Christian, of all who saw her, came nearest to making the correct diagnosis. He believed that all her difficulties were probably on the basis of a vascular disturbance. He thought that she gave a fairly consistent history of intermittent claudication and that the redness of the feet of which she then complained was not unlike that described by Weir Mitchell as erythromelalgia. It was his opinion that the neuritic manifestations were secondary to some form of vascular disease.

The intermittent nature of the disease, with certain definite exacerbations and remissions, is well illustrated by the patient's weight chart during the course of her illness. On the whole, the remissions were of short duration and by no means complete. The course of the disease appeared slowly progressive. The prognosis was obvious many months before the diagnosis was established.

The patient entered the Robert Dawson Evans Memorial on March 15, 1937 and stayed there almost continuously until her death, in November 1938. It was not until January 1938, or ten months after her entry, that the diagnosis of periarteritis nodosa was established. The manner in which this came about is of some interest.

In the Robert Dawson Evans Memorial, as elsewhere, a great many diagnoses were suggested. The clinical picture was striking enough; the patient had peripheral neuritis, intermittent bouts of fever with abdominal cramps and diarrhea, cutaneous lesions that came and went and a beefy red tongue. Yet for a long time no one had sufficient clinical imagination to correlate all these findings logically under the definition of one disease.

In August Dr. T. J. C. Von Storch suggested that the patient might have hypertrophic interstitial neuritis and that a bit of the peroneal nerve be excised for biopsy. When this was done, the neuropathologists who were consulted agreed that the excised nerve did not show changes characteristic enough to substantiate the diagnosis.

The patient was badly discouraged. She seemed to be making no headway and was ready to try anything. She had been examined repeatedly in the hunt for possible foci of infection. Since the shadow of the gallbladder was not visualized after intravenous injection of dye, Dr. Howard Clute agreed to abdominal exploration in the hope that removal of a possible focus of infection, such as a diseased gallbladder, might be followed by a remission such as had

TABLE 2.—*Weight Curve in Periarteritis Nodosa, Illustrating the Relapsing Nature of the Disease*

Date	Weight, Kg.
1933	71
1934	63
1935	49
Tonsillectomy	
1936	61
1937	61
1938	47
1938	36
Cholecystectomy	
1938	46

occurred earlier, after tonsillectomy. On entering the peritoneal cavity he discovered a gallbladder with many stones in it, which he removed; he also performed incidental appendectomy. He described the stomach and the upper part of the duodenum as seemingly edematous and containing multiple areas of hemorrhage throughout and the transverse and descending colon and cecum as diffusely injected and slightly thickened. The significance of these findings was not realized at the time.

Comment.—In retrospect, two unrelated episodes stand out as being pertinent to the case. Not long ago one of us attended a clinical-pathologic conference at the Massachusetts General Hospital. Dr. J. H. Means remarked, as the record of a patient whom he had seen in life was discussed by one of the younger clinicians, how much easier it often is to make brilliant diagnoses from a "paper case" than in reality. This certainly was true in the case of M. K. As one reads the record it seems peculiarly stupid, in the light of the correct diagnosis, that four years should have been necessary to establish it. In clinical medicine, as in other things, hindsight is often better than foresight.

For twenty-five years Dr. H. A. Christian has repeated over and over to his interns and residents that in order to remain keen and with sharpened wits they must read: old medical literature, current medical literature and all other kinds of medical literature. The wisdom of this advice also is well illustrated by the case of M. K.

In January 1938 a review on periarteritis nodosa was submitted to the Editorial Board of the *Archives of Internal Medicine* by Dr. Linn J. Boyd of New York. Thus one of us was presented, so to speak, with the diagnosis of M. K.'s disease in a neatly labeled package, for as Dr. Boyd's review was studied it was obvious that the diagnosis of periarteritis nodosa fitted M. K.'s story perfectly. The gallbladder, appendix and peripheral nerve sections were reexamined; each showed characteristic lesions of periarteritis nodosa, and thus the proper diagnosis was finally determined. During the patient's subsequent stay in the Robert Dawson Evans Memorial she went downhill gradually and

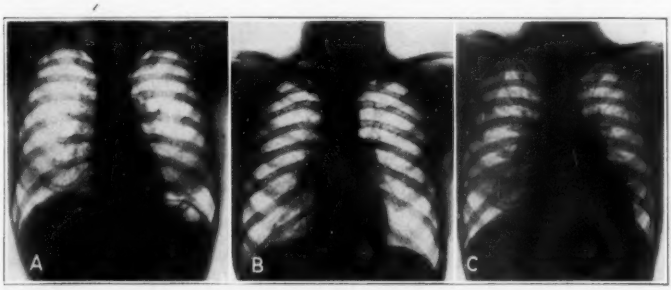

Fig. 1.—Increase in transverse diameter of the heart shadow. *A*, roentgenogram taken in November 1936. The aorta was 4.7 cm. in diameter, and the width of the heart was 10.6 cm. *B*, roentgenogram taken in November 1937. The aorta was 5.5 cm. in diameter, and the width of the heart was 11 cm. *C*, roentgenogram taken in November 1938. The aorta measured 5.5 cm. in diameter; the width of the heart was 16.2 cm., and the heart weighed 460 Gm.

at last died. A variety of bacteriologic studies carried out in an attempt to discover some cause for the disease gave entirely negative results.

At necropsy the most striking single feature was the fact that in almost every section of every tissue examined one could observe periarterial lesions at all stages of their development: early degenerative lesions, acute inflammatory lesions and chronic or healed perivascular infiltrations around small blood vessels. The initial inflammatory lesion appeared to be acute, with neutrophilic infiltration. This was followed by infiltration of lymphocytes or eosinophils and eventually by the development of dense fibrous perivascular scarring. Apparently the process would begin in one small artery, run its course, develop in a neighboring vessel and run its course; and whatever caused the disease obeyed no set rules or regulations. Thus it was that the patient presented manifestations of a peculiar, slowly pro-

gressive and at times intermittent disease in practically every system of the body, strikingly in the circulatory system, the renal system, the gastrointestinal tract, the nervous system, the hematopoietic system and the skin.

Clinically the heart sounds always were normal so far as signs of valvular disease were concerned and their quality was not abnormal. The cardiac rate, as in Kussmaul and Maier's case, tended persistently to be rapid. As time went on the heart enlarged to a surprising degree, and despite the fact that the heart muscle was diseased signs of congestive failure or of pain in the heart did not develop, nor did striking electrocardiographic changes occur.

The almost spectacular manner in which the cardiac shadow enlarged is well illustrated by roentgen measurements. Until January 1938 there was little change. But from then on something occurred to make the heart shadow increase in size rapidly, as manifested by a progressive change in transverse diameter from 12 cm. in January to 16.2 cm. in November.

Electrocardiographically all that happened at first to suggest heart disease were transitory changes in the T wave in lead I; this wave would become almost

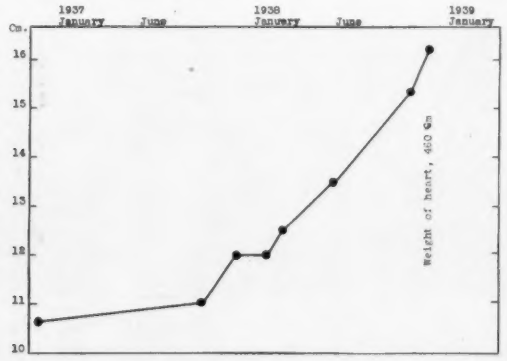

Fig. 2.—Graphic representation of the progressive increase in the diameter of the heart shadow as measured roentgenographically.

isoelectric for a time, later to revert to its normal shape. Even three weeks before death, when a notable change in the state of the heart had occurred, the tracing still was essentially normal. The last tracing, taken shortly before death, showed clearcut abnormalities in the T wave and in the S-T segments.

That no significant congestive failure occurred is shown by the fact that in February 1938 the venous pressure was 55 cm. of water, and in November, three weeks before death, it was 82 cm. of water. In August the vital capacity was 2,800 cc., and in November, 2,200 cc. There never was orthopnea. On the whole, despite the fact that organically the patient had advanced disease of the heart muscle, she had little to show for this in the way of symptoms or signs.

The heart weighed 460 Gm. The myocardium throughout was firm, dense and fibrous, cutting with difficulty. Scattered through it were numerous irregular areas of dense gray fibrous scar tissue averaging 2 to 3 mm. in diameter and having a shotty feel due to areas of old perivascular infiltration. The larger coronary branches, however, showed no irregular beading or distinct morphologic change, and their interior was smooth and glistening. The valves were normal.

Histologically, surface sections through various portions of the heart showed varying degrees of organizing pericarditis. The mesothelial cells were for the most part intact, but at occasional points the pericardium was roughened by torn fibrous adhesions consisting of rather highly vascular old connective tissue infiltrated with and containing small clumps of lymphocytes and plasma cells. Elsewhere the pericardium presented small areas of contracture in which the many newly formed capillaries were markedly engorged and the edematous, relatively recently formed connective tissue was heavily infiltrated with lymphocytes, plasma cells and monocytes, many of the last-mentioned cells containing hemosiderin. There were also occasional eosinophils. The larger coronary branches in the pericardium showed varying degrees of endothelial thickening of their intimas and fibrosis of their walls, particularly in the region of the adventitia. On pro-

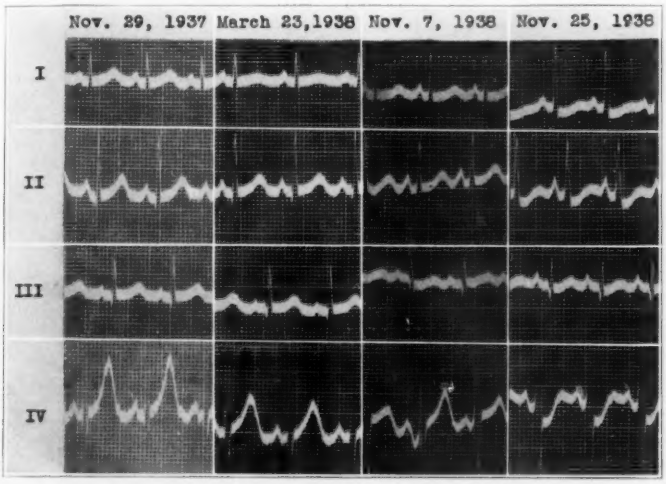

Fig. 3.—Electrocardiographic changes during the course of periarteritis nodosa.

gressing through the myocardium extensive areas of old fibrous scars and a few small areas of more recently formed ischemic necrosis were encountered. The connective tissue throughout was edematous and infiltrated with small numbers of lymphocytes and endothelial cells. Nothing resembling Aschoff bodies was seen. The smaller arterioles showed a varying picture. In places their lumens were practically obliterated by endothelial hyperplasia of the intima, fibrosis of the media and profound fibrosis of the adventitia. About such vessels were rare lymphocytes. Rare small arterioles were present, showing alterative degenerative changes. In these the intima was lined with fibrin, the endothelium was edematous and there were a necrotizing process of the media and adventitia and surrounding edema. There was no cellular infiltration. The aorta showed a fibrous and hyaline thickening of its intima, beneath which were small deposits of atheromatous material. Its media was intact and showed no histopathologic change in the

sections at hand. Its vasa vasora, however, showed granulating and healed arteriolar lesions. In none of the blood vessels examined were any aneurysms observed grossly or microscopically.

The blood pressure behaved surprisingly. Little by little it tended to become elevated, but there was a cyclic course to its curve, as though whatever caused hypertension would do so in bouts and suggesting that when the stimulus to hypertension was relieved the blood pressure reverted to normal.

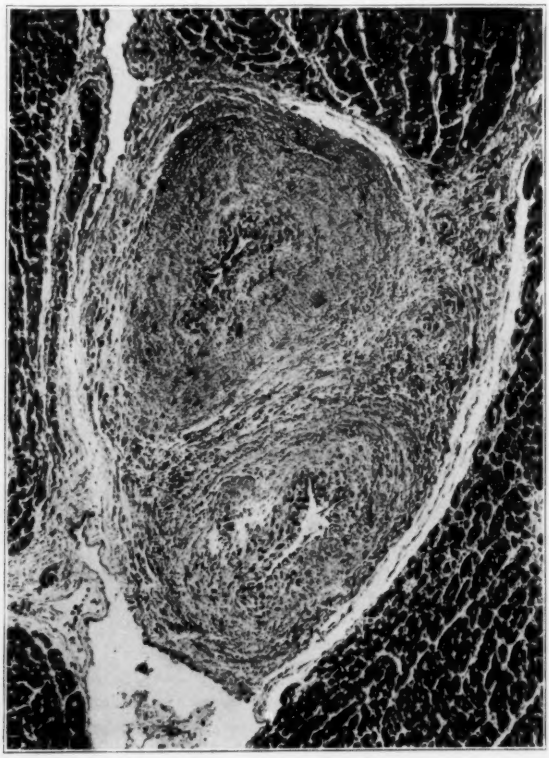

Fig. 4.—Healed lesion of periarteritis nodosa from the interventricular septum near the apex of the heart, showing extreme scarring of the entire wall and fragmentation of the elastica, with little regeneration, and proliferation of the intima. Only rare acute lesions were observed in the heart. × about 177.

That the kidneys had much to do with the level of the blood pressure and the eventual development of persistent hypertension is suggested by the changes that developed in these organs.

The combined weight of the kidneys was 260 Gm. On section, the surface of each was irregularly pitted, the intervening nodular areas standing up as pale pinkish or yellowish gray zones averaging 5 mm. in diameter. The normal

relation between the pyramids and the cortex was distorted, though reasonably well preserved. At the upper pole of the right kidney was a small area having all the characteristics of a single infarct. The capsule was firmly adherent. The pelvis showed somewhat thickened epithelium, and the ureter was thickened and dilated. The renal arteries and veins were thickened but showed no atheromatous plaques or marked narrowing of their lumens. The large artery as it entered the hilus was fully two-thirds obliterated by dense fibrous thickening of its intima, which had in places torn or made irregular the underlying internal elastic membrane. About this vessel there was also considerable perivascular scarring.

Sections through various portions of the kidney showed varied pathologic change. All four phases of vascular lesions were present, and the pathologic picture of the adjacent parenchymatous units was directly predicated on the type

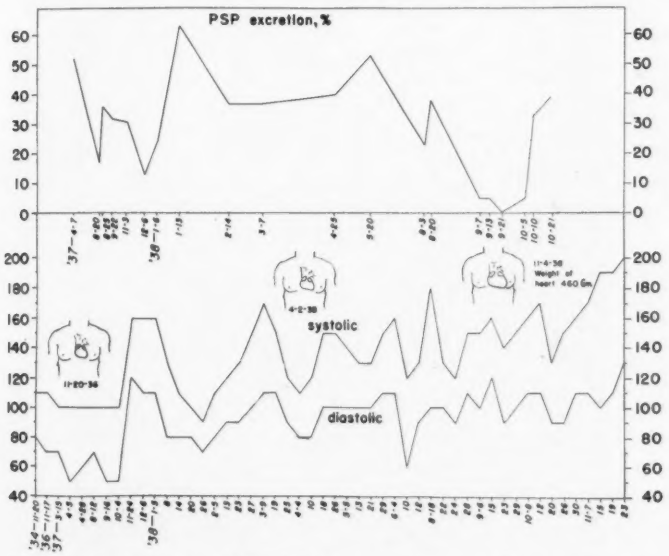

Fig. 5.—Varying phenolsulfonphthalein excretion and blood pressure curve during the course of periarteritis nodosa.

of vascular lesion with which it was associated. The old healed lesions obviously created areas of dense scarring similar to healed infarcts; the acute lesions caused acute glomerulitis or acute interstitial nephritis with destruction of the included tubules. In little involved areas the tubular epithelium was swollen, stained faintly acidophilically and showed various stages of karyolysis and karyorrhexis. The collecting tubules almost uniformly contained hyaline or granular casts and not infrequently blood casts. Many seemingly intact and functional glomeruli were present. Others showed some capsular proliferation or fibrous thickening of the glomerular tufts. In general the efferent and afferent arterioles were intact, but where they were involved in necrotizing arteriolitis the glomerulus showed a picture either of acute hemorrhagic glomerulitis or of profound neutrophilic infiltration.

Clinically this peculiar renal lesion appeared to be characterized by exacerbations and remissions of transitory attacks of acute nephritis. The urine from time to time contained varying degrees of albumin, and a few red or white cells would appear in the sediment. There never was any increase in the nonprotein nitrogen content of the blood. Renal function, however, as judged by the excretion of phenolsulfonphthalein, varied tremendously. Presumably, had the process kept up long enough, terminal renal insufficiency would eventually have developed.

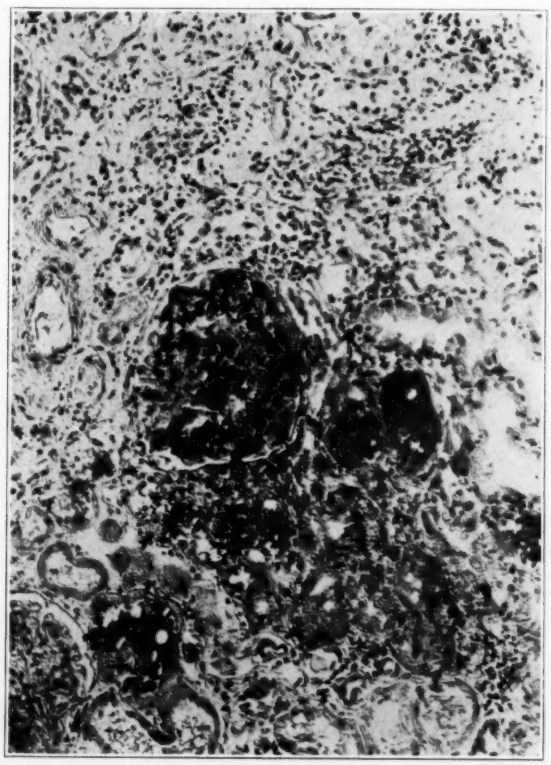

Fig. 6.—Section of the kidney, showing focal glomerulitis resulting from acute periarteritis nodosa involving the afferent arteriole. Note the uninvolved glomerulus near by. Both kidneys showed numerous early, advanced and healed lesions of the smaller arterioles, with concomitant involvement of the affected parenchyma. The main artery at the hilus was reduced by healed lesions to one-third its normal size. × 144.

In this particular instance, however, between the attacks of what amounted to acute nephritis due to the vascular disease enough normal renal tissue was left to maintain good renal function.

The increased capillary resistance resulting from periarteritis of the smaller renal vessels was probably an important factor in the development of hypertension. Possibly the intermittent nature of the hypertension was due to patchy destruction of the renal cortex. This causation is in line with Goldblatt's experiments.

The intestinal lesions were striking. Clinically, as has been stated, the patient complained of intermittent attacks of pain and diarrhea. These attacks might or might not be accompanied by fever. Repeated roentgen examination of the gastrointestinal tract revealed no evidence of intrinsic pathologic change. The stools never contained anything abnormal and for the most part gave no evidence of loss of blood; occasionally a moderately positive reaction to a benzidine test would be reported. That the patient was able to absorb ordinary foods was apparent because, as the weight curve revealed, she gained weight after tonsillectomy in 1936 and after cholecystectomy in 1938. While she was under observation,

TABLE 3.—*Behavior of Gastric Hydrochloric Acid*

	Cc. of Tenth-Normal Acid per 100 Cc. of Gastric Juice			
		Minutes After Alcohol Meal		
Date	Fasting	15	30	45
July 31, 1935	29	88	80	60
April 6, 1937	41	41	46	55
Aug. 18, 1937	15	10	34	34
June 2, 1938	0	0	13	29

TABLE 4.—*Sugar Tolerance Tests*

	Blood Sugar, Mg. per 100 Cc.				
Date	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
April 13, 1937	76	138	161	99	120
Sept. 4, 1938	91	153	211	181	142

however, there developed a diminution in the ability of the stomach to excrete free hydrochloric acid in response to an alcohol test meal, the dextrose tolerance appeared to diminish and she continually lacked vitamin C.

The behavior of the gastric hydrochloric acid is shown in table 3.

Two dextrose tolerance tests were completed, one in April 1937 and one in September 1938. The results were so unlike as to be worth mentioning.

The concentration of ascorbic acid in the blood always was below 1 mg. per hundred cubic centimeters, and in September 1938 a saturation test carried out according to the technic of Wright, Lilienfeld and MacLenathen[2] revealed only 46 per cent excretion, in contrast to a normal value of about 90 per cent.

The protein metabolism appeared to remain normal. The nonprotein nitrogen content of the blood did not become abnormally low, and, more important still, the plasma proteins showed relatively little change. To be sure, there was a slight falling off in the albumin content of the plasma, but never enough to cause reversal of the albumin-globulin ratio or a critical fall in the total protein level.

2. Wright, I. S.; Lilienfeld, A., and MacLenathen, E.: Determination of Vitamin C Saturation, Arch. Int. Med. **60**:264-271 (Aug.) 1937.

The data given in table 5 appeared to us of considerable interest. One gets the impression that the patient could not store vitamin C, although she was able to absorb proteins and sugar normally. We attempted to determine whether she was able to absorb fat normally by employing 500 cc. of 20 per cent cream as a test meal and estimating the cholesterol and fat concentration of the plasma at later intervals. Unfortunately some of the fat meal was vomited, so that the results of the test are not wholly convincing. However, the figures are reported for what they may be worth. One gets the impression that some of the fat, at least, was normally absorbed. Why was it that in an intestine capable of absorbing protein, fat and sugar comparatively well, vitamin C seemingly should have been absorbed with difficulty?

The appearance of the intestinal tract was striking. It is remarkable that so few symptoms developed in the presence of so extensive a lesion.

TABLE 5.—*Level of Plasma Protein in Grams Per Hundred Cubic Centimeters*

Date	Total Protein	Albumin	Globulin
April 12, 1937	6.4	4.7	1.7
Nov. 29, 1937	7.6	4.6	3.0
April 5, 1938	7.7	4.9	2.8
June 10, 1938	7.5	5.1	2.4
Aug. 19, 1938	7.1	3.9	3.2
Oct. 21, 1938	6.2	3.5	2.7

TABLE 6.—*Fat Tolerance Test,* Oct. 3, 1938*

	Blood Cholesterol, Mg. per 100 Cc.	Total Fat Content of Blood, Mg. per 100 Cc.
Fasting	141	442
2 hours	165	
4 hours	171	
6 hours	133	842
8 hours	162	

* Five hundred cubic centimeters of 20 per cent dextrose was given by mouth.

The rugae of the stomach were poorly defined. Near the pylorus were two minute patches, each approximately 1 cm. in diameter, over which the mucosa was flattened. Beginning with the duodenum and extending through the small intestine and the entire colon was thickening of the intestinal wall by edema. The mucosa presented hundreds of ulcerative lesions in all stages of formation. The early lesions averaged about 1 cm. in diameter, were round and were no more thickened than was the surrounding mucosa. The next most advanced lesions were oval and circumferentially arranged, almost but not quite encircling the intestine. These lesions averaged 2.5 cm. in length and 1.5 cm. in width and were eroded; over them the serosa was thickened, telangiectatic and not infrequently roughened by wisps of yellow fibrin. The most extensive lesions were an accentuation of this process. Sometimes the advanced ulcers measured 4.5 cm. in length and 2 cm. in width. They showed no heaping up or induration of their edges. They had irregular nodular bases. They were limited peripherally by a broad zone of necrotic mucosa, and the entire intestinal wall and the overlying peritoneum were involved in the lesions. Yet there was no evidence of perforation or near perforation in any of these areas.

Sections through the esophagus and the cardiac end of the stomach showed marked submucosal edema throughout. Although the esophagus was grossly normal, it showed foci of necrosis of the surface epithelium, beneath which there was definite infiltration of lymphocytes, eosinophils and rare monocytes. The blood and lymphatic vessels were distended. The arterioles of this section, particularly in the region of the serosa, showed definite early degenerative changes. The adjacent (cardiac) end of the stomach showed massive coagulation necrosis, the mucosa, submucosa and muscularis being only faintly outlined. Extensive acute arterial lesions were present, varying from edema, swelling and necrosis of the wall to massive neutrophilic infiltration. Areas of frank necrosis of the muscularis were present, heavily infiltrated with neutrophils, particularly in the periarterial region; about such areas the capillaries were markedly engorged.

Section throughout the small and large intestine corresponded more or less identically with the gross anatomic findings. The early mucosal lesions were associated with early arterial lesions, while the more advanced mucosal lesions and frank erosions were associated with definite areas of acute arteritis. Many of the larger mesenteric arterioles were partially occluded by recently formed fibrin thrombi. Their media and adventitia were edematous, contained fibrin and were heavily infiltrated with neutrophils, eosinophils, endothelial cells and lymphocytes. There were surrounding capillary engorgement and definite proliferation of capillaries and fibroblasts. Over such vessels the adjacent peritoneum showed well defined localized peritonitis. Only rare arterioles showed any evidence of completely healed lesions.

Sections through the pancreas were interesting. For the most part the acini and islands were perfectly intact and presented a normal histologic appearance. There was, perhaps, a slight ingrowth of fat cells. Examination of the arterioles disclosed all four phases of the lesion associated with the disease at hand, acute arteriolitis predominating. One of the larger arterioles present, fully 1 mm. in diameter, was completely occluded by an organizing fibrin thrombus. Half of the wall showed practically no histopathologic change, while the other half was in an advanced state of organizing acute arteritis, with fibrin, neutrophils and endothelial cells prominently displayed. Healed lesions were rare in the sections at hand, only two vessels being materially affected. These, however, presented only minute, pinpoint lumens, the remainder being replaced by dense fibrous thickening of the intima with some scarring of the media and marked scarring of the adventitia.

The liver weighed 1,910 Gm. It was soft and boggy, but the normal lobulations were well defined. The capsule was not thickened. The cut surface showed normal lobulations sharply accentuated beneath a light yellowish brown background, and this was distinctly friable and contained irregularly mottled yellowish gray areas suggesting patches of necrosis. Histologically the picture was diffuse and varied. In general, the sinusoids, particularly about the central veins, were distended with red cells, and occasional pericentral areas of replacement fibrosis suggested the terminal reaction to chronic passive congestion of some duration. At numerous points throughout the parenchyma were minute areas of focal necrosis in which the liver cells showed varying degrees of degeneration and neutrophilic infiltration.

Examination of the periportal connective tissue showed that considerable and relatively uniform damage had been occurring for some time in this zone. There were many healed arteriolar lesions with considerable surrounding fibrosis, which in places had impinged on the bile ducts, causing frank capillary bile stasis. At least two of the vessels in the section examined showed well defined

granulating lesions with virtually complete obliteration of their lumens by endothelial cells, fibroblasts and newly formed capillaries. Other vessels showed early lesions with edema, endothelial thickening, early deposits of fibrin and necrosis of their walls. There was only one vessel which showed really acute arteriolitis.

The neurologic findings were difficult to evaluate; they were notably bizarre, diffuse and inconstant. At no time were there any mental symptoms.

Historically, the first symptoms began as paresthesias involving the face. In 1934, more than four years before death, the pupils were fixed and irregular, the

Fig. 7.—Section of the pancreas, showing acute periarteritis nodosa with thrombosis, edema, fibrinous exudate and heavy infiltration of neutrophils, lymphocytes and rare eosinophils. Note spilling of the process into the adjacent parenchyma. × 147.

tongue was deviated to the left, the right biceps jerk was greater than the left, and the abdominal reflexes, the knee jerks and the ankle jerks were absent. A little more than a year later, a weakness of the right facial nerve developed, and now there also was a readily apparent stocking distribution of hypesthesia and hypalgesia, complicated by bilateral foot drop, by atrophy of the leg and foot muscles, and by weakness of the leg muscles.

After tonsillectomy all this was followed by several months' remission. During this time the patient felt better than for a long time; she gained in strength and complained only of occasional pain in her feet.

In the fall of 1936 a second relapse occurred. In the spring of 1937, when the patient first was examined in the Robert Dawson Evans Memorial, the neurologic picture was that of extensive polyneuritis. There was peripheral loss of sensation to pain, temperature and touch on the inner aspects of the arms and below the level of the middle part of the legs. There was a small area on the upper anterior surface of the left thigh where sensation to touch alone was lost. There was marked atrophy of the muscles of the hands and feet. There was partial foot drop. The brachial reflexes were diminished, and the reflexes in the legs were absent. No fibrillary twitchings were observed. Sweating on the right side of the face and scalp at times was pronounced.

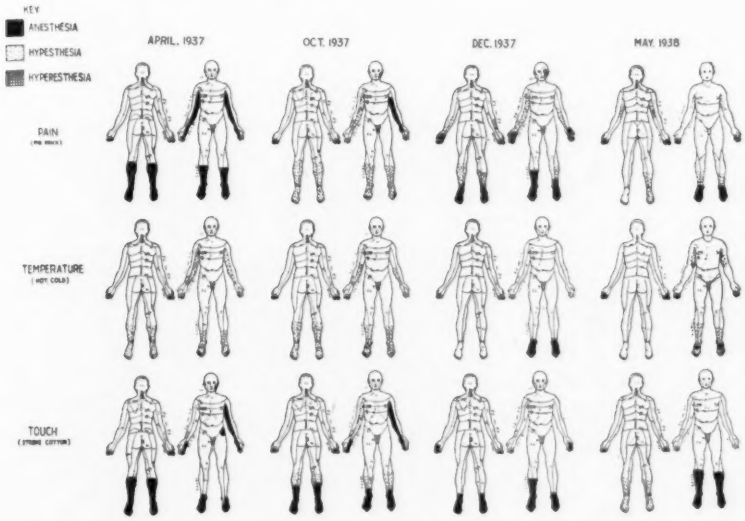

Fig. 8.—Varying sensory changes observed during the course of periarteritis nodosa.

The pupils still were irregular, the left being larger than the right, and there still was weakness of the right facial nerve. As time went on the peripheral signs varied considerably; atrophy of the truncal muscles as well as of those of the extremities took place. Relapses and remissions of sensation (fig. 8) along the peripheral nerves occurred, in all probability as new nutrient arteries to nerves were involved and went through the pathologic cycle described in other vascular areas.

Toward the end there developed transient diplopia; the optic disks, which hitherto had been normal, became choked, and a massive retinal hemorrhage appeared in the right fundus.

Throughout the course of the illness the spinal fluid showed little change. Perhaps there was a tendency for the protein to increase as the disease progressed and for the colloidal gold curve to shift to the left.

At necropsy the brain was not examined, but the spinal cord and various peripheral nerves were studied. Grossly the cord appeared normal except for a well defined engorgement of the vessels throughout. Histologically the arterioles both within and without the parenchyma of the cord were involved in healed and organizing lesions. The peripheral nerves showed the same process. The fine arterioles traversing the nerve bundles were involved in inflammatory processes. In places they showed early arteriolitis; in other places, acute or healed arteriolitis. Not infrequently the acute inflammatory process seemed to extend through the nerve sheath and to some extent to involve adjacent fibers.

The effect of the disease on the hemopoietic system was striking. In 1935, three years before her death, the patient had moderate secondary anemia with a value for hemoglobin of about 60 per cent and a red blood cell count of 4,000,000 per cubic millimeter. During her stay in this hospital the hemoglobin level ranged between 60 and 80 per cent, the red cell count remaining fixed in the neighborhood of 4,000,000. Liver, iron and transfusions made no difference. There appeared to be persistent low grade anemia which responded to no form of therapy. The sedimentation rate remained increased. The white blood cell count,

TABLE 7.—*Spinal Fluid Findings*

Date	Protein, Mg. per 100 Cc.	Colloidal Gold Curve
Nov. 19, 1934	23	0 0 0 0 0 0 0 0 0 0
July 31, 1935	20	1 1 1 1 1 0 0 0 0 0
April 12, 1937	20	1 1 2 2 2 2 1 0 0 0
Oct. 25, 1938	42	2 2 3 2 2 1 0 0 0 0

on the other hand, varied from day to day, as might have been expected from all the acute lesions that existed from time to time. It ranged from 7,000 to 22,000 per cubic millimeter. When leukocytosis appeared there was regularly an increase in the proportion of polymorphonuclear leukocytes. We were unable to detect any marked eosinophilia, such as has been described in other cases. Occasionally 3 or 4 per cent of eosinophils was encountered. No abnormal forms of white cells were ever seen.

Grossly, the bone marrow appeared normal. On histologic examination sections from the marrow of the femur, vertebra and sternum all showed arterioles having marked fibrous thickening and representing a healed lesion. They also presented smaller arterioles showing early lesions, endothelial thickening and arteriolar necrosis, as well as minute arterioles showing acute lesions about which the bone marrow predominately was infiltrated with neutrophils and eosinophils.

The spleen weighed only 120 Gm. and appeared normal. In spite of its relatively normal size and gross appearance, however, it showed marked histopathologic change in its arterioles. In general the capsule and pulp were not remarkable. The germinal centers were well defined and showed none of the phenomena customarily associated with acute or toxic splenitis. The arterioles showed a variety of changes. Some showed well defined edema of the intima with protrusion of the endothelium and necrosis of the remainder of the wall. Others showed marked acute arteritis, the lumen being filled with organizing blood and the wall being edematous and massively infiltrated with neutrophils, some fibrin, occasional eosinophils, monocytes and plasma cells. This infiltration

extended through the adventitia into the surrounding pulp, where foci of true acute splenitis were formed. In such areas eosinophils were frequent. Still other vessels presented well defined zones of organization, the intimal and medial thickening being definitely replaced by granulation tissue. Still other vessels were in a completely healed stage of dense general fibrosis with almost total obliteration of the lumens. Sections of lymph nodes from various portions of the body presented vascular lesions identical with those observed in the spleen.

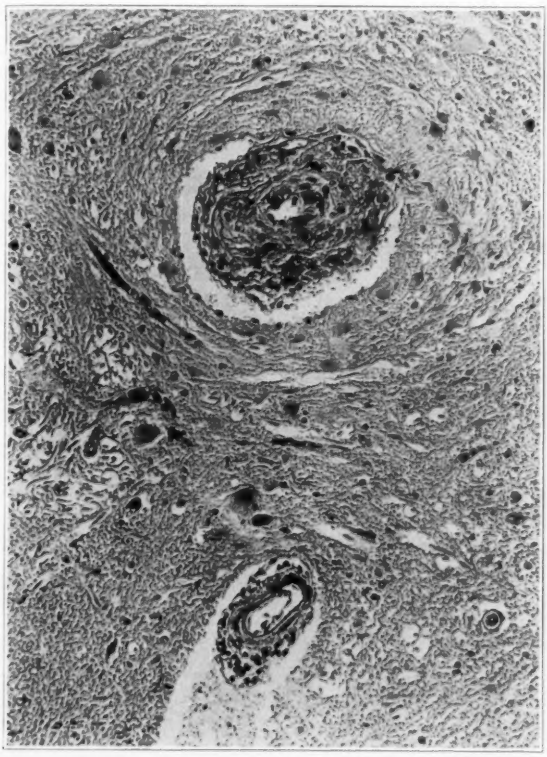

Fig. 9.—Segment from the lower thoracic portion of the cord, showing acute periarteritis nodosa of an arteriole of the posterior horn, with an adjacent branch not involved except for perivascular cuffing with lymphocytes. Acute and healed lesions were noted throughout various levels of the cord, with surprisingly little pathologic change in the parenchyma. × about 228.

The cutaneous changes were varied. As early as 1934 (four years before death) there developed erythematous lesions on both feet followed by pigmentation. In 1937, after cholecystectomy, the skin over the abdomen and the lower parts of the legs acquired a peculiar blotchy appearance, and the skin over the incision took months to heal. Early in 1938 the face and neck became pigmented. A few

months later urticaria-like lesions over the trunk developed from time to time. Finally, during the last few months there appeared on the forearm tender, evanescent pulsating nodules surrounded by areas of erythema or purpura.

At necropsy a characteristic cutaneous lesion was removed. Immediately below the left antecubital fossa the skin presented an irregular nodular elevation approximately 1.5 by 4 mm. The underlying tissue was distinctly injected. The surface epithelium was intact, and the immediately adjacent corium showed little histo-

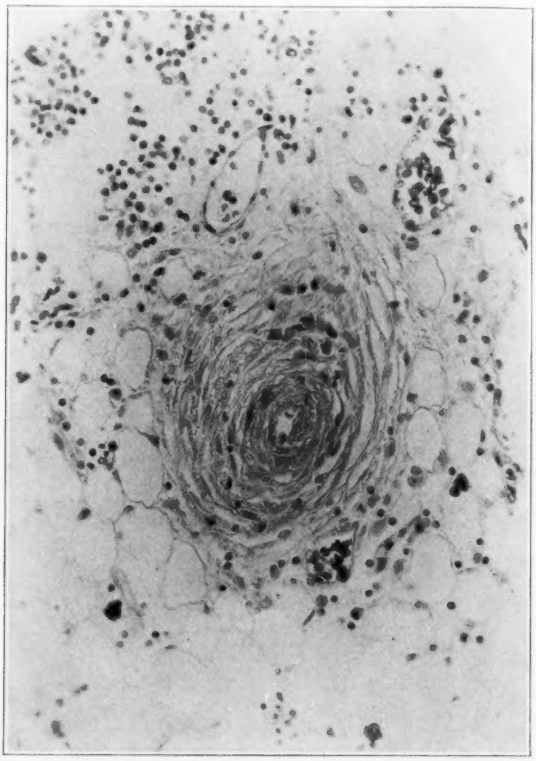

Fig. 10.—Femoral bone marrow, showing the early stage of periarteritis nodosa with endothelial proliferation, edema of the wall and neutrophilic infiltration. Sections from sternal, vertebral and femoral marrow all showed early and healed lesions. × 238.

pathologic change. The fibrofatty tissue, however, contained arterioles in which early, acute and healed lesions were observed.

One puzzling clinical finding was the manner in which the basal metabolic rate behaved. It tended to be elevated, but in an intermittent fashion. There were no other signs of hyperthyroidism, and the basal metabolic rate was never con-

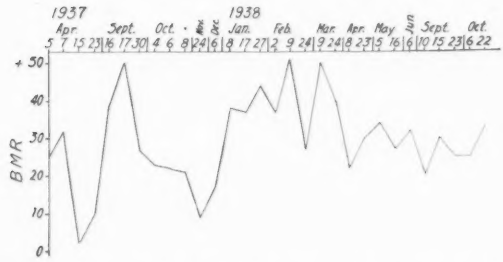

Fig. 11.—Varying basal metabolic rate during the course of the disease.

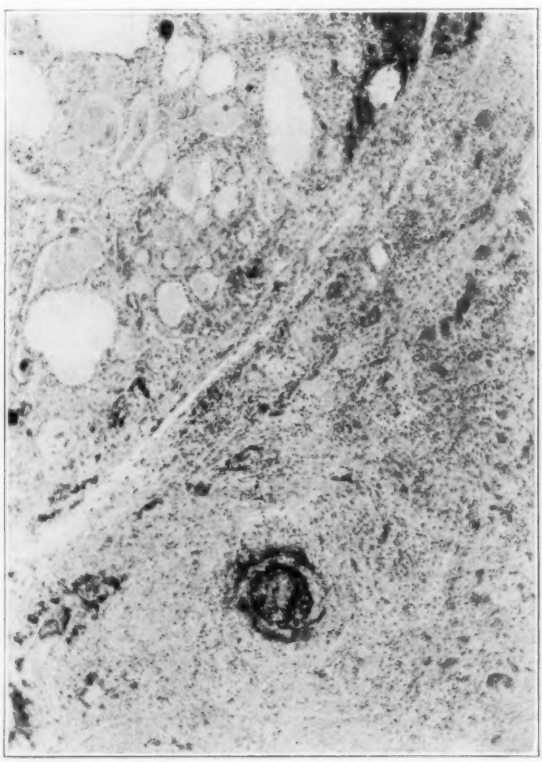

Fig. 12.—Section of the thyroid in a case of acute periarteritis nodosa, showing numerous old and recent lesions, all of which involved the adjacent parenchyma to some extent. × 73.5.

sistently influenced by iodine. The trend of the metabolic rate was as eccentric as the blood pressure level and the renal function.

Neither the thyroid nor the adrenal glands appeared grossly remarkable, yet each showed periarterial lesions.

Sections through the thyroid showed the acini to be relatively uniform in size and shape, filled with normally staining colloid material and exhibiting no evidence of secondary hyperplasia. Careful examination of its stroma, however, revealed numerous vessels affected by the disease process. Occasional vessels showed profound fibrosis and a healed stage. The most extensive lesions, however, were acute; in these the arterioles were partially to completely occluded by fibrin thrombi, their edematous walls being infiltrated with fibrin, many neutrophils, some endothelial cells, lymphocytes and rare eosinophils. There was definite capillary proliferation about the periphery of such vessels. One or two of the arterioles presented a striking picture, one side being entirely normal while the other half was massively involved in profound acute arteriolitis.

The vessels about the periphery of the adrenal glands also showed acute arteriolitis with fibrin thrombi, edema and fibrin deposits in the wall and infiltration with neutrophils, lymphocytes, endothelial cells and (rare) eosinophils. Similar lesions were occasionally seen in the vessels of the medulla. About these areas there were small foci of necrosis.

In 1933, it will be remembered, the patient complained of an irritating, nonproductive cough which lasted for a long time. During the months that she was under our observation, however, cough was never an important symptom. Thus, clinically the pulmonary system was the one system in which there was no sign of pathologic activity. From this point of view the pathologic description of the lungs is especially significant.

The lungs together weighed 1,020 Gm. Grossly they showed no significant change. The great vessels were normal. On histologic study the bronchi showed no specific inflammatory processes. Careful examination of numerous vessels throughout showed well defined, healed arteriolar lesions in the form of dense medial and adventitial fibrosis. At no point in the sections observed were we able to see any acute or organizing arteriolitis. A few of the larger arterioles showed edema of the intima with swelling and protrusion of the endothelium. There was also edema of the media and adventitia. The remainder of the lung showed little evidence of pathologic change beyond the accumulation of albuminous coagulum within the aveoli.

COMMENT

This case is reported as of especial interest because the patient was under careful observation for so long a time. All our findings are typical; they bring out little new.

Certainly the history of periarteritis nodosa disposes to clinical humility. In the seventy-three years which have elapsed since Kussmaul and Maier described the case of Carl Seufarth, little that is significantly new has been added to the general knowledge of the disease. Kussmaul and Maier deserve full credit for recognizing a new clinical syndrome, a clinical picture which, as they said, became the more perplexing the longer it was observed and with a prognosis likely to be evident long before the diagnosis could be established.

Even with the old-fashioned and crude methods of histologic study at their disposal, they gave an adequate description of the nodular thickening which they found so characteristically around countless small arteries in their case, and they believed that the disease commenced acutely in the media of these small arteries, all other clinical and pathologic manifestations being secondary to this fundamental lesion.

In our case the pathologic observations well confirmed the clinical findings. The intermittent, prolonged course of the illness and all its symptoms can be explained by the peculiar jumble of acute, subacute and chronic or healed vascular lesions which were seen in nearly every tissue examined.

Kussmaul and Maier were no less humble than we when it came to saying what might cause such a disease. Since their time many theories have been put forward. No one, however, has succeeded any better than

XXIII.

Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht.

Von

Prof. A. Kussmaul und **R. Maier**

in Freiburg i. Br.

Hierzu Taf. III—V.

Krankengeschichte.

Carl Seufarth von Gernsbach, 27 J. alt, Schneidergeselle, kam 4. Mai 1865 Morgens 10 Uhr in die medicinische Klinik zu Freiburg. An dem ziemlich mageren Menschen fiel die ungemein blasse Farbe von Haut, Lippen, Mund-

Fig. 13.—Title of a paper published in 1866 and containing the first description of periarteritis nodosa.

they in determining the nature of the agent which injures so remarkably the smaller vessels of various organs and which causes such an extraordinary clinical picture. Until the causative agent is found, little can be said of treatment.

It is interesting that Kussmaul and Maier drew attention to the fact that certain patients with periarteritis nodosa may recover spontaneously. They saw Landolin Faust, who fell sick in August 1864 with an illness much like Carl Seufarth's. Faust, however, grew better and recovered to some extent. In August 1865, biopsy of a bit of muscle was done, and this showed periarterial lesions comparable with the lesions observed in the case of Seufarth. Kussmaul and Maier recorded this experience and warned against the possible danger of biopsy in such cases; the wound from this minor operation required eight weeks for complete

healing, a situation comparable to that is our case, in which the gall-bladder incision failed to heal completely for many months. Nowadays, too, the disease need not be entirely hopeless, and occasionally the patient may recover. This is illustrated by the case of C. W. P., a patient whose medical adventures Dr. Albert R. Parkhurst of Beverly, Mass., has been kind enough to summarize for us and allow us to report.

C. W. P. was 39 years old in 1932 when he first entered the Beverly Hospital. His history was uneventful except that for a little over a year he had been bothered by asthma. His sinuses and antrums contained polyps, which were duly treated. General physical examination otherwise gave negative results. It was noted that on one occasion on his first admission to the hospital the white blood cell count was 17,000 per cubic millimeter, with 7 per cent eosinophils.

In 1933, about a year later, he suddenly had a violent headache with pain under both shoulders and a stiff neck. He reentered the hospital and was found to have normal blood pressure, normal physical findings except for asthmatic rales in both sides of the chest, a strongly positive Kernig sign, discrete glands palpable in the neck, axillas and groins, a choked disk on the left side and grossly bloody spinal fluid under greatly increased pressure. He was hospitalized for a month, growing better with repeated spinal punctures. During this time the white blood cell count ranged between 12,000 and 15,000 per cubic millimeter; there was no eosinophilia. The urine varied in gravity and occasionally contained albumin and a few red or white cells in the sediment.

In 1934 he again felt ill and reentered the hospital. For several months after leaving he had been comfortable and fairly active, but by degrees his legs became stiff, his feet began to ache, and finally a peculiar variety of cutaneous lesions developed. The cutaneous lesions were variously described as being of five types: hemorrhagic, nodular, bullous, urticarial and eczematous. The nodules were largest on the forehead, with smaller areas over the back of the hands and the dorsa of the feet. Accompanying the nodules were enlarged glands in the axillas and in the groins. His pain was striking. Even at rest his feet were extremely painful, and the pain appeared to be deep seated rather than superficial. On this admission to the hospital there were inexplicable bouts of crampy abdominal pain with or without diarrhea, and areas of anesthesia and hyperesthesia were noted over the upper parts of both legs. He remained in the hospital for several weeks; occasionally he had slight fever; the white blood cell count ranged between 18,000 and 45,000 per cubic millimeter. Usually the predominant leukocytes were polymorphonuclear, although on one occasion 50 per cent eosinophils were noted; the urine was normal except for an occasional trace of albumin and for rare red cells and granular casts in the sediment; there was no hypertension, and the Wassermann reaction was repeatedly negative.

One of the subcutaneous nodules and at least one of the nasal polypi which had been removed from time to time revealed vascular lesions consistent with the diagnosis of periarteritis nodosa.

The patient gradually grew better and six years later was entirely well except for asthma. There had been no recurrence of cutaneous lesions, of cerebral symptoms, of leg cramp or of abdominal pain. About all that was appreciably left of his illness was slight weakness and hyperesthesia of the left hand and left thigh and hands and feet which felt the cold more easily than is normal.

He died suddenly in an asthmatic attack. Necropsy revealed a rare healed lesion around the smaller arterioles in the heart, the kidneys and the intestinal tract. On the whole, the striking feature revealed by the examination was the miraculous manner in which all active lesions of periarteritis nodosa seemingly had disappeared.

Periarteritis nodosa remains much as it was when first described. It is a freakish vascular disease of unknown origin, likely to prove fatal within a few weeks or months from the time it first causes symptoms, producing extremely varied clinical manifestations and not yet subservient to any specific form of prevention or cure.

CHRONIC MALARIA

A CLINICAL CONSIDERATION

GEORGE H. FONDÉ, M.D.
AND
EDGAR C. FONDÉ, M.D.
MOBILE, ALA.

Malaria is a chronic disease, not alone an infection of the blood stream characterized by chills and fever. Failure to comprehend or detect its insidious course and its strong tendency to relapse, even after months or years, accounts for the fact that it still ranks as one of the serious social and economic problems. Some authors [1] have recognized the persistent and prolonged course of malaria; nearly all acknowledge it to be the most widespread and destructive of tropical diseases. Because in its chronic form it is generally disguised, the problem of control is doubly hard to master.

We are not concerned here with early "classic" forms of malaria. These conditions constitute the minority and are largely limited to well known regions; they offer little or no difficulty in diagnosis and are easily controlled, temporarily at least, by specific treatment. Moreover, in these early infections plasmodia can usually be demonstrated (except in hyperpyrexial, cerebral and "blackwater" forms).[2]

On the other hand, in dealing with chronic malaria the physician is confronted with a complex problem. In this stage the disease is not easy to recognize, and it is difficult to demonstrate the parasite. The chronic infection is generally masked under syndromes closely resembling a number of common local and systemic diseases. In all cases it tends to become asymptomatic, whether treated or not, during some phase of its course.

INCIDENCE

First, it should be pointed out that there are no geographic limitations to the chronic forms of malaria, as contrasted to early typical infections, which are largely confined to endemic zones. From a study of 10,000 malarial patients in the dispensaries of Odessa, U. S. S. R., Korovitskiy [3] concluded that chronic malaria does exist in temperate

1. Heiser, V.: An American Doctor's Odyssey: Adventures in Forty-Five Countries, New York, W. W. Norton & Company, Inc., 1936.

2. Mackie, T. T.: Personal communication to the authors.

3. Korovitskiy, L. K.: The Problem of Chronic Malaria, Vrach. delo **19**: 359, 1936; abstracted, J. A. M. A. **104**:470 (Aug. 8) 1936.

climates where reinfection is not possible. According to his data not more than 40 per cent of patients were cured at the end of four years. The greater number of cases of chronic involvement usually escape recognition, especially when removed from malarial regions. There is now reason to suspect that in this day of constant travel to and from areas of inoculation more patients with chronic malaria are to be found outside the endemic regions than among the static populations; the condition is not recognized, largely because of the mistaken impression that a change of climate alone will effect a cure. Such an infection is generally regarded as having been eradicated, despite recurrence of atypical symptoms, and the impaired health passes for injury done rather than for disease still present. Petritz,[4] from a study of malaria in Illinois, was convinced that there were between 15,000 and 25,000 cases of chronic malaria in that state, in most of which the condition was unrecognized and untreated. If this is an index of its prevalence, what must be the total number of cases of chronic involvement unrecognized and untreated in the whole of the United States? Statistics officially published on the incidence of malaria are generally based on demonstration of parasites rather than on clinical evidence. We believe that such statistics are by no means a true indication of the extent of malaria.

CLASSIFICATION

Chronic malaria may be divided into two clinical types.

1. *Reactive Chronic Malaria.*—The reactive type is that in which the defensive forces are more or less vigorously operative. This type embraces a latent, an atypical and a typical late phase.

In the latent phase the progress of the disease is arrested because of the prompt destruction of parasites by a highly developed immune mechanism.[5] Vigorous and well nourished subjects may appear to be in fair general health when reactivations have not been too frequent or persistent. Such patients are usually ambulatory. Even those whose general health is obviously impaired often refuse to believe that they are subjects of a chronic infection, because the progress of the disease has been so insidious. They rarely seek medical attention; their condition remains unrecognized; a lower level of vigor is casually regarded as an individual characteristic or idiosyncrasy, rather than the result of a chronic disease.

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4. Petritz, L. J.: Chronic Malaria: Some Clinical Aspects, Illinois M. J. **44**:193, 1936.

5. Taliaferro, W. H., and Cannon, P. R.: The Cellular Reactions During Primary Infections and Superinfections of Plasmodium Brasilianum in the Panamanian Monkey, J. Infect. Dis. **59**:72, 1936.

The atypical phase, manifested in the great majority of all cases of chronic involvement, always produces definite symptoms, although these symptoms are extremely varied. The clinical manifestations depend on localization of the colonies of parasites in fixed tissues (reticuloendothelial cells) and vary according to the extent of toxic and allergic effects as well as to individual susceptibility to them. On account of the prevailing concepts of what is required for diagnosis, malaria in this phase is often overlooked. There is sufficient phagocytic and humoral immunity to destroy circulating parasites, which accounts for the absence of typical symptoms in these patients.

The typical late phase is seen in patients who have lost their power to resist parasitic invasion of the blood stream. However, the parasites may not be demonstrable in the peripheral blood in the first few days of this phase; they are more frequently discovered at the end of twenty-four hours, after the third typical paroxysm. We have often noticed the reappearance in the blood smear of large numbers of both schizonts and gametocytes.

2. *Nonreactive Chronic Malaria.*—In the nonreactive type the patient is extremely ill, disabled and confined to bed. The infection has advanced to a dangerous point, and the patient's defensive powers are exhausted. His body fails to react characteristically to malarial proteins released at the time of segmentation; hence the diagnosis is difficult. These are often called "quinine-fast cases."[6] Demonstration of parasites is rarely possible, and the absence of parasites is presumed to be the result of severe toxemia. The temperature is normal or subnormal for the greater part of the time; the patient is at or near the cachectic stage, which is characterized by advanced organic degeneration, and the related symptoms frequently disguise the long-existent primary cause. Subjects in a cachectic state of chronic malaria often have a dry, copper-colored skin, which is an important diagnostic point when the history discloses early attacks occurring over a number of years. This type of malaria is commonly observed in children before the development of immunity as well as in persons enfeebled by age who have lost their relative degree of immunity.

DIAGNOSIS

A practical diagnosis of chronic malaria rests on the results of four methods of investigation, namely, taking of an exhaustive history, a complete physical examination, specific drug tests and laboratory procedures.

6. Pais, A.: Radio-Stimulation in the Treatment of Malaria, in Contributions to Radio-Stimulative Therapy, series 1 and 2, Rome Instituta de radio-eccitamento, 1926; Radio-Stimulation in the Treatment of Malaria: Radion, ibid., series 4, 1928.

A study of the history should be directed mainly toward exclusion or confirmation of previous attacks of malaria. Exposure to inoculation and previous acute attacks would suggest the possibility of persistence and chronicity of the infection. When the evidence (previous frank attacks, positive diagnosis or previous treatment) points toward malaria, the burden of proof in differential diagnosis becomes reversed; i. e., it becomes necessary to disprove the presence of malaria before other considerations are taken up. Such a method of evaluation of the patient's status with regard to a previous infection obtains with syphilis. It should likewise be regarded as of the greatest importance with malaria, which has similar relapsing tendencies. The late H. R. Carter made the statement, "Its duration in man, if not eternal, is indefinite."[7] Sir Ronald Ross stated that his father had typical malaria seven years after leaving the region of possible reinfection.[8]

Notation of the time at which exacerbations occur is of great assistance in recognizing the periodicity, or rhythm of recurrence, of symptoms. In early malaria the usual interval for the two tertian varieties of parasites is approximately forty-eight hours. Such a frank invasion is readily confirmed by microscopic demonstration of the parasites in all stages of incubation (exceptions already mentioned). On the other hand, the periodicity manifested in the atypical phase, as observed clinically, is seven to ten days.[9] This regular recurrence is aptly illustrated by the ocular forms of malaria, in which the symptoms are clearcut both subjectively and objectively. As far as we can ascertain, no explanation has been offered to show why exacerbation of symptoms in atypical malaria should occur at the seven to ten day interval. It is reasonable, however, to suppose that the vegetative cycle of the parasites is delayed in the more shaded and protected lodgments as compared with the fuller exposure to the activating influence of sun and light on circulating parasites. Deaderick[10] stated:

> Relapses at short intervals have been recognized since the time of Hippocrates. Later the "septenary" periods were noted for tendencies to show relapses, and this

7. Carter, H. R., in Maxcy, K. F.: Epidemiological Principles Affecting the Distribution of Malaria in Southern United States, Reprint 920, United States Treasury Department, Public Health Service, 1924, p. 3.

8. Ross, R.: The Prevention of Malaria, London, John Murray, 1910.

9. One of us (G. H. F.) recalls that the seven to ten day periodicity in afebrile chronic malaria was first brought to his attention by his preceptors. Great emphasis was placed on the pathognomonic evidence of periodic supra-orbital unilateral neuralgia in old cases of malaria. Attention was called also to the frequency of other periodic neuralgias in afebrile malaria as diagnostic and as specifically responsive to quinine.

10. Deaderick, W. H.: A Practical Study of Malaria, Philadelphia, W. B. Saunders Company, 1909.

idea is still largely prevalent among the laity. This is also in accord with the observation of Cohen and Trielle. They state that this period is 5 to 21 days, usually 5 to 10 days, and that the relapses may consist of one or more typical malaria paroxysms, or they may be atypical.

Recent research has thrown new light on this aspect of the subject, revealing and probably removing the points of disparity between clinical knowledge of the disease and the life cycle of the parasite in human beings. The first important fact pertains to schizogony in reticuloendothelial cells. On March 18, 1937, James and Tate [11] demonstrated before the Royal Society of Tropical Diseases and Hygiene of Great Britain the full vegetative cycle in the endothelial cells lining the brain of the domestic fowl. This experiment was made with the avian strain of the parasite but will probably prove to be a working basis for understanding malaria in human beings. The second fact is the experimental demonstration of the latent phase of the disease. Taliaferro and Cannon in their brilliant work on primary infections and superinfections have shown that the development of phagocytic activity renders the disease asymptomatic in spite of the fact that parasites reproduce at the same rate. Their experiments were carried out with Panamanian monkeys, and Plasmodium brasilianum [5] was used.

These two discoveries, we believe, are epoch making. They reaffirm and establish the importance of clinical interpretation rather than dependence on laboratory findings, which has long been emphasized. The possibility of a vegetative cycle in man and the certainty of latency will do much to correlate the knowledge of the many parts of the problem of chronic malaria into one continuous and comprehensive whole. The well recognized periodicity (forty-eight hours for tertian varieties, seventy-two hours for quartan) is subject to many alterations. When multiple infections are present or when mixed varieties of parasites coexist the clinical picture is less definite. The symptoms are related to overlapping of the respective cycles. The reproduction of parasites in fixed tissues may again modify the periodicity. The diagnosis may be facilitated if the clinician carefully determines the time relations of the earliest paroxysms. We shall mention later the employment of "specific drug tests." This early clinical behavior is especially important in the estivoautumnal variety of infection. In this type a remittent rather than an intermittent recurrence of symptoms is noted except in the first two or three paroxysms. When this tertian infection becomes pernicious, the seizures progressively anticipate by two or more hours the regular time of occurrence. The increasing virulence is further manifested by a longer duration of the attack. They are then without intermission and without frank remission. Thus, a "closing up"

11. New Light on the Life-Cycle of the Malaria Parasite, editorial, Lancet **1**:764, 1937.

of the intervals conceals the abrupt beginning time of segmentations, and the improvement noted in the intervals between early paroxysms is lacking. We have repeatedly observed this pernicious course in atypical malaria as well as in the classic forms. Such a development is generally supposed to occur with the third paroxysm, and we believe that it should be recognized in time to avert the extremely critical complications.[12]

Punctual exacerbation of symptoms is a distinctive characteristic of malaria. In the bacterial diseases the symptoms usually attain their maximum gradually toward the latter part of the day. In malaria, however, there is an abrupt onset, generally within two hours of noon. These seizures coincide with the release of malarial toxins and merozoites. Pronounced improvement in the intervals between attacks has often influenced us in favor of malaria rather than toward an abdominal disease requiring operation or some other acute disease. We have often been aided in making a diagnosis by noting the astonishing coincidence of relapse in old known cases and the influx of new ones. A wavelike prevalence of the condition is seen in the spring and fall and following extraseasonal rises in temperature.

On inspection, the subject with chronic malaria of recent activity discloses a muddy subicteric tint of the skin and scleras. The tongue is broad and coated, often showing marginal indentations made by the teeth. There is a general pallor of the mucous membranes. The spleen in all cases of chronic involvement is notably affected. The majority of patients present prolapse of the organ with definitely increased splenic tension, which is especially noted on the day after a paroxysm. Usually the spleen is palpable at or several inches below the costal margin. In order to differentiate enlargement or prolapse of the spleen from other causes, the patient should be carefully palpated on successive days, and the findings should be correlated with periodic recurrences already discussed. Abdominal examination is best accomplished when the stomach and colon are empty. Percussion is a valuable adjunct to palpation, replacing the latter for obese or muscular patients.

Specific drug tests are decidedly the most valuable methods of detecting malaria in atypical and latent phases. The provocative test consists of one day of full dosage with either quinine or atabrine (an acridine dye). Recognizable symptoms will be brought about within a few days to three weeks, especially if the test is carried out during the

12. In cases of acute involvement this clinical characteristic was often seen during the Spanish-American War. Among the Michigan and Illinois troops were many patients with febrile and "algid" comatose forms of malaria. These forms were confused with uremic coma, owing to the associated nephritis, until parasite demonstration was made in a few cases. Other patients had severe chills an hour or two before becoming unconscious.

seasons of expected reactivation. The therapeutic test consists of one full week's course of atabrine or quinine. Marked relief from symptoms and improvement of the general condition within the following week or ten days indicates probable malaria. A confirmation of the diagnosis would be made by a sharp and more characteristic return of the periodic symptoms. In the atypical phase this test is modified by administering the specific drug to cover three successive seven day cycles (according to the therapeutic program which we shall propose). The fullest response is generally noted after the fourth week; the fourth paroxysm would not appear, but marked improvement is soon observed.[13] These specific drug tests are contraindicated for patients whose vitality is extremely low.

The employment of "protein shock" and the use of epinephrine and other agents, such as hot baths, have been recommended to facilitate the demonstration of parasites in the blood. We have not found such measures effective in enabling us to find the parasite, but they are decidedly helpful in aiding clinical recognition of latent and atypical phases of chronic infection.

Every patient should have the benefit of a general examination of the blood in addition to careful and repeated search for plasmodia. The degree of anemia and injury to blood cells often reveals important evidence. The most frequent indication incriminating malaria is stippling of the red cells twenty-four hours after an attack and marked increase of eosinophils. For indications of long-standing damage from the infection, poikilocytosis and other evidence of the injured hemopoietic organs are often noticed. The Bass-Jones concentration test has yielded the greatest success in demonstrating the parasites in blood smears. We have found the reaction to be positive more frequently when the blood is taken twenty-four hours after the occurrence of the atypical symptoms. The Henri melanoflocculation test has been of aid in a smaller number of cases.

DIFFERENTIAL DIAGNOSIS

A previous history of chronic malaria with seasonal relapses is the most important consideration in diagnosis. As with syphilis, the manifestations of chronic malaria are so protean that the symptom complex of almost any disease can be simulated. Therefore, we believe it to be impractical to give here a more detailed method of differential diagnosis than has already been suggested. However, it is worth while to list some conditions with which chronic malaria may be confused or in which it may play the primary etiologic role.

13. Statistics recently reported (Gill, D. G., and Smith, M.: Atabrine as a Malarial Prophylactic Agent: Experiment with the Drug in Central Alabama, J. M. A. Alabama **8**:66, 1938) support this clinical interpretation.

TREATMENT

There is undoubtedly a need for collective treatment of persons who are unable to obtain individual clinical guidance. Without discrediting such collective methods, "standardized" procedures have dulled the judgment of clinicians in general and obscured the importance of chronic malaria in the population. We object to the prevailing system of treatment for five reasons: 1. Heavy saturating doses are employed

Table of Conditions

System	Disease	Syndromes	Symptoms
Gastrointestinal (of greatest frequency)	Cholecystitis; uncinariasis; vitamin deficiencies; sprue; typhoid fever; typhus fever; undulant fever; late syphilis	Hepatitis; allergies;* Addison's disease; catarrhal jaundice; Banti's disease; amebic infection	Pain over right lobe of liver; nausea or vomiting near noon; distress and fulness about throat and neck; abdominal, focal and surgical symptoms; diarrhea; dysentery
Nervous system: (2d in frequency)	Psychoneurosis; encephalitis	Neurasthenia; epileptiform seizures; migraine-like headaches; neuralgias	Insomnia; phobias; headaches; syncope; herpes simplex; herpes zoster; vertigo; globus hystericus; tremors
Circulatory-blood: (3d in frequency)	Blood dyscrasias; agranulocytosis;† leukemias; essential hypertension; hypotension; Raynaud's disease; purpura; symptomatic anemias	Urticaria; angioneurotic edema	Anginoid pains; faintness and vertigo; tachycardia
Genitourinary	Pyelitis; hemorrhagic nephritis	Hematuria; hematinuria; uremia and uremic coma	.....
Respiratory	Pneumonia; asthma	Bronchitis (recurring)	.....
Ocular	Unilateral glaucoma; keratitis punctata; chorioretinitis	.....	.....
Bone and Muscular	The arthritides	Lumbago; torticollis	Articular, muscular and osseous pains
Endocrine	Gonadal deficiency; thyrotoxicosis	.....	.....

* The coincidence of chronic malaria and hay fever and asthma syndromes has been noted in a large proportion of cases in children and adolescents (Fondé, G. H.: Clinical Aspects of Hay Fever and Asthma, J. M. A. Alabama **1**: 471, 1932).

† Fondé, E. C., and Fondé, G. H.: Allergy as the Direct Etiological Factor in Malignant Granulopenia: Clinical Study Based upon One Fulminant Case, J. M. A. Alabama **3**: 375, 1934.

in a chronic disease. 2. Treatment is based on the idea that destruction of parasites in the circulating hemocytes removes the infection from the fixed tissues also. 3. The individual follow-up treatment of an inveterate relapsing disease is not taken into account.[13a] 4. Employ-

13a. Angus McDonald (Malaria Problems of Today, in Nelson's Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1926, vol. 7, pp. 299-345) reported that 10 grains (0.65 Gm.) of quinine daily for thirty days is followed by relapse in 30 per cent of cases within two months. He further states that while absolute removal of parasites from the blood, therefore, "a parasite cure," cannot be guaranteed thus, yet the subjugation of relapse is a matter of taking quinine, and the termination of relapse is proportionate to the period of taking quinine.

ment of these standardized systems is too frequently based only on the demonstration of parasites. 5. Satisfactory control of the disease is not effected in a great majority of cases of chronic involvement. Therefore, we believe that there is urgent need to revise the concepts of treatment. The plan presented here, in our experience, has proved to be a far more satisfactory method of treatment than the standardized methods and is not open to the objections which have been cited.

The plan is designed to take care of certain considerations which are extremely important in the successful management of chronic malaria. The fundamental principle is to administer the specific drugs so that the maximum concentration will be present in the blood when the merozoites are released. This concept is generally adhered to but too often is inadequately carried out because the treatment is insufficiently prolonged. Neglect of this necessity is probably due to the fact that the occurrence of atypical symptoms has not been recognized as an indication for therapy. Furthermore, the appearance of symptoms may be approximately calculated in advance if careful study is made of past recurrences so that the most effective time for drug therapy can be predetermined. Such administration of specific drugs greatly aids the natural phagocytic response by diminishing the number of merozoites; thus it also prevents an excessive release of malarial proteins and degradation products, which would result in toxic and allergic shocks to the liver and other vital organs. Lastly, but of great importance, general debility of the patient and exhaustion of the hemopoietic system are prevented.[14]

GENERAL MEASURES

The patient should remain in bed during the febrile stage. The diet should be light during administration of large doses of quinine or atabrine. Purgation is employed to facilitate proper absorption and tolerance of these drugs; this is effectively accomplished by small doses of mild mercurous chloride and sodium bicarbonate followed by a saline purgative. Alkalinization is desirable, and for this one of the effervescent alkaline salt combinations is used. (Sinton has shown that a patient with malaria requires several times more alkaline salts to render the urine neutral than does a normal subject.) Sedation is usually required at the beginning to alleviate the discomfort and psychic disturbance caused by the specific drug.

SPECIFIC MEASURES

As the management of chronic malaria demands a prolonged plan of treatment, we prefer to employ atabrine and quinine in alternate

14. Fondé, E. C., and Fondé, G. H.: Allergy as the Direct Etiological Factor in Malignant Granulopenia: Clinical Study Based upon One Fulminant Case, J. M. A. Alabama **3**:375, 1934.

courses provided there is no contraindication to either drug. Quinidine sulfate may in some cases be substituted for quinine if the latter is objectionable. Our experience convinces us that atabrine in general is decidedly the most effective agent and is better tolerated in effective doses than quinine. Because atabrine is more slowly eliminated it stands guard against fresh entry of merozoites into the fixed tissue cells for a longer time than does quinine, and therefore relapses are less frequent with the former drug. Atabrine also has a special virtue in infection by Plasmodium falciparum and in other pernicious forms of malaria. On the other hand, atabrine should not be given too frequently, on account of its cumulative effect and the discoloration which it produces in the skin.

Objection has been made to atabrine on the ground that it is sometimes responsible for inducing psychoneurotic symptoms or aggravating those already commonly present in chronic malaria. We believe that this does occur, particularly in "cerebral cases." However, it is our opinion that focal reactions in the brain are comparable to the Herxheimer effect in syphilis under specific treatment. We have long observed that after the definite aggravation of symptoms on institution of treatment there was a remission of psychic disturbances. We have been gratified to note that in general the psychoneurotic subjects who have previously been afebrile and unresponsive to treatment have had a periodic temperature curve and have improved markedly with treatment.

We have abandoned the use of plasmochin as a therapeutic agent because of its extreme toxicity (see comment on epidemiologic value).

The doses given will naturally vary somewhat with the individual case, depending on the body weight and general vitality of the patient as well as on his response to treatment.

OUTLINE OF TREATMENT

Attack Period (to abate the early paroxysms).—The following drugs and quantities may be given.

Days	
1-3	Atabrine, 1½ grains (0.09 Gm.) three times a day, or Quinine sulfate, 10 grains (0.65 Gm.) three times a day
4-5	Rest period
6-8	Atabrine, 1½ grains (0.09 Gm.) twice a day, or Quinine, 10 grains (0.65 Gm.) twice a day
9-10	Rest period
11-12	Atabrine, 1½ grains (0.09 Gm.) twice a day, or Quinine, 10 grains (0.65 Gm.) twice a day

Maintenance Period.—The following drugs and quantities are correct for this period.

Days	
14-20	Rest period
21-23	If atabrine was employed previously, quinine sulfate, 10 grains (0.65 Gm.) at midnight If quinine was employed previously, atabrine, 1½ grains (0.09 Gm.) twice a day
24-30	Rest period
31-33	Atabrine, 1½ grains (0.09 Gm.) twice a day
34-40	Rest period
41-43	Quinine, 10 grains (0.65 Gm.) at midnight

[NOTE.—When quinine has been found objectionable, atabrine should be given in one full course at the beginning of treatment (15 tablets of 1½ grains [0.09 Gm.] each). Atabrine should then be omitted for at least two weeks before the half-course (seven tablets of 1½ grains [0.09 Gm.] each) is given. Subsequent half-courses of atabrine should be spaced four, five, six, seven and eight weeks apart, according to the season, for reasons previously explained.]

Consolidation Period.—This alternating use of quinine and atabrine continues with the rest period increasing by one week up to four weeks (early spring, summer and fall months) and up to eight weeks (winter months). During rest periods injections of iron and arsenic or bismuth compounds are given. These are almost as important in the treatment of chronic malaria as are the specific drugs. We prefer to avoid the free use of arsenic in cases in which there is evidence of serious impairment of hepatic function. We therefore employ half-courses of iron and arsenic, either intramuscularly or intravenously, in the form of cacodylate of iron, a 1 grain (0.06 Gm.) ampule every four days until six are given. This may be alternated with intramuscular injections of a bismuth compound, also in half-courses (six doses) at four day intervals. Injections of bismuth subsalicylate in oil are started to establish tolerance to this drug. The drug may be given in aqueous solution for subsequent doses, which causes less pain locally but is more rapidly eliminated. If indicated, succeeding half-courses are spaced progressively further apart. Liver extract is of value in hemopoiesis, thus combating anemia. We wish to stress that general supportive measures and good hygiene are necessary. Easily digested foods which have a high vitamin and mineral content should be prescribed. In case of malaria in which there is damage to the liver, liberal quantities of warm water containing small doses of sodium phosphate (taken two hours before breakfast) stimulate better flow of bile and intestinal evacuations.

NONREACTIVE MALARIA

The guiding principle in the management of nonreactive malaria is improvement of the vital condition of the patient by employment of supportive measures as previously mentioned. Specific drugs should be cautiously administered. It is important to check the leukocyte count, which should improve after the administration of quinine or atabrine. If the leukocytes are decreased the specific drugs should be withheld. They may be resumed with caution after an increase in the white cell count is noted. A very light exposure to roentgen rays is claimed to be an effectual substitute for the well known "mountain air and altitude" in its effect on the hemopoietic tissues.[6]

The necessity of repeated readjustment of the schedule of therapy should be kept in mind; these readjustments are made on the slightest evidence of reactivation. In many cases reinauguration of the "attack period" is indicated.

Experience has taught us that in most cases it is necessary to extend the treatment of malaria over a period of two to three years. As with all chronic diseases, the complete cooperation of the patient is absolutely essential for the success of the treatment. The patient should record the time at which the slightest suggestion of a return of recurrent symptoms of the same character as during previous attacks takes place. The time of new symptoms should also be recorded. We name this a "diary and calendar system." It should include the patient's schedule of treatment. All patients should be kept under close clinical supervision as long as any active evidence of the disease exists. They should be asked to report for examination with their records at progressively longer intervals.

COMMENT ON EPIDEMIOLOGY

Attention is directed to the significance of two recent reports in regard to the inadequacy of present methods of approach in preventing the spread of malaria. First, malaria in the United States, according to statistics during the past decade, shows a steady rise in the mortality rates and a greater extension in the endemic areas northward and westward from the so-called malarial zones.[15] This is true notwithstanding vastly increased expenditures and more exhaustive research. Second, the Commission of the League of Nations on Malaria has reported that eradication of malaria from a community by prophylactic treatment with drugs is virtually impossible. The report goes on to say, however, that it is desirable to provide adequate and easily available

15. Faust, E. C.: Malaria Mortality in Southern United States for the Year 1936, South. M. J. **31**:816, 1938.

treatment for the clinical manifestations of the disease so that the morbidity, mortality and physical incapacitation of the afflicted persons may be diminished.[16]

We believe that the solution of the problem as applied to a community lies in thorough treatment of the individual patient. We thereby are directing our efforts toward eradication of the sources of infection (plasmodia carriers) which are so abundantly supplied by patients with the active and chronic conditions. Plasmochin in minute doses is recommended by some authorities as an efficient agent for removing the circulating gametocytes, so that infection of the mosquito is less likely to result. In cases in which there is persistence of gametocytes after the first intensive course of treatment, we have employed plasmochin, 1/6 grain (0.01 Gm.) at three day intervals until plasmodia are no longer found.

Certain groups are recognized as particular hazards to malaria communities by reason of greater virulence resulting when they become infected and greater numbers of gametocytes develop for mosquito transmission. We refer to the unacclimated members of the population and to children, who are thought to be prolific sources for the dissemination of malaria,[16] presumably because of their relatively low degree of immunity.

It is therefore urged that the physician consider malaria in the light of public health and that the public health officials adopt a system whereby close cooperation between physician and official is assured, in order that an adequate check-up can be made on all cases of malaria.

SUMMARY

The concepts of diagnosis and treatment presented in this article are based on a study of malaria during forty-two years of active practice. Many of the same cases were under observation for periods ranging from fifteen to thirty-five years. A large percentage of the cases were of the estivoautumnal variety.

Chronic malaria is the most prevalent form of the disease; it has no strict geographic limitation, and it is largely unrecognized and untreated.

Various clinical phases of malaria are described and suggestions for their recognition are given. In this connection it is pointed out that the atypical phase is most frequently seen.

Objections to "standardized treatment" are cited, and a plan of treatment obviating these objections is presented.

Finally, comment is made on the epidemiologic value of thoroughly treating the individual patient.

16. The Treatment of Malaria, Fourth General Report of the Malaria Commission, Bull. Health Organ., League of Nations **6**:897, 1937.

CONCLUSIONS

Chronic malaria is essentially a persistent infection with a strong tendency to relapse seasonally and extraseasonally in lowered states of vitality. For a practical diagnosis of chronic malaria greater dependence must be placed on the clinical history and on the clinical manifestations.

In the treatment of chronic malaria, control of virulence and arrest of progress of the infection is effected by a prolonged follow-up. Brief courses of specific drugs, spaced in accordance with the periodic releases of merozoites, to prevent breaking down of phagocytic defense by overpowering multiplication of parasites, and the employment of general measures of vital support are the principal means of controlling the disease in the individual.

Control of malaria in communities rests mainly on effective control of the volume and virulence of the malaria organisms exposed to mosquito transmission by prompt and thorough treatment of all infected persons. This method recommends itself because it is in accord with the natural laws operative against the spread of malaria as of other diseases. It would be more desirable than eradication of the infection in populations exposed to inoculation, and it would at the same time control the morbidity, the mortality and the incapacitation resulting from malaria.

BIOPHOTOMETER TEST AS INDEX OF NUTRITIONAL STATUS FOR VITAMIN A

GRACE STEININGER, M.S.
AND
LYDIA J. ROBERTS, PH.D.
CHICAGO

After the report by Jeans, Blanchard and Zentmire [1] that the biophotometer may be used to measure a subject's nutritional status for vitamin A, work was begun in this laboratory, as in many others to test its usefulness for this purpose. The present article reports the results of over 2,000 biophotometer tests of 459 subjects—194 adults and 265 children during more than a year of experimentation. These tests have been made on subjects with both good and poor diets, with and without supplements on subjects kept for long periods on diets deficient in vitamin A and on subjects with very high levels of vitamin A intake. Furthermore, the reading for subjects on the depletion diets have been correlated with the amount of vitamin A found in the blood. The purpose of the testing has been to determine first the reliability of the test and then its validity as a measure of vitamin A stores. The results of the biophotometer studies are reported in this article; those of the studies of the blood in another publication.[2]

Since the literature on this subject has been reviewed by others, the review will not be repeated here. Suffice it to say that reports from eight additional laboratories on the use of the biophotometer have appeared. Two of these [3] confirmed the findings of Jeans and his associates; three [4] gave what may be termed qualified confirmation; and in

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From the Department of Home Economics, the University of Chicago.

1. Jeans, P. C.; Blanchard, M. S., and Zentmire, Z.: Dark Adaptation and Vitamin A, J. A. M. A. **108**:451-458 (Feb. 6) 1937.

2. Steininger, G.; Roberts, L. J., and Brenner, S.: Effect of a Depletion Diet on the Vitamin A in the Blood of Normal Adults, J. A. M. A., to be published.

3. Jeghers, H.: The Degree and Prevalence of Vitamin A Deficiency in Adults, J. A. M. A. **109**:756-762 (Sept. 4) 1937. Corlette, M. B.; Youmans, J. B.; Frank, H., and Corlette, M. G.: Photometric Studies of Visual Adaptation in Relation to Mild Vitamin A Deficiency in Adults, Am. J. M. Sc. **195**:54-64 (Jan.) 1938.

4. Schuck, C., and Miller, W. O.: Dark Adaptation of the Eye and Vitamin A Storage in Young Adults, Arch. Int. Med. **61**:910-915 (June) 1938. Gridgeman, N. T., and Wilkinson, H.: Night Blindness and Vitamin A Deficiency, Lancet

(Footnote continued on next page)

three[5] it was stated that the biophotometer test is unreliable and of doubtful value for diagnosing vitamin A status. The evidence at present, therefore, appears to be about equally for and against the usefulness of the test. It is significant to note, however, that the two most extensive and well controlled studies—those of Palmer and Isaacs—are in the negative group. Nevertheless, one cannot ignore the positive findings of the other workers that subjects with low readings have improved on vitamin A supplementation and that in 2 subjects (1 of Jeghers' and 1 of Booher's) a diet deficient in vitamin A caused marked impairment in dark adaptation, the subsequent addition of a supplement resulting in rapid improvement. It is clear, however, that these results must be repeated in tests of larger numbers of subjects under carefully controlled conditions before the usefulness of the test in practical nutrition can be demonstrated. The present study represents a contribution to this aspect of the problem.

METHOD

The biophotometer and the technic of its use were described in full by Jeans and his associates.[1] A brief statement of the theory back of the test and the chief points of the method which are essential for an understanding of the present article will be given.

The test is based on the theory that ability to see in the dark is dependent on the presence of visual purple in the retina. When the eye is exposed to a bright light the visual purple is bleached and the visual threshold is raised. The speed and amount of regeneration of visual purple in the dark is believed to be dependent in part on the presence of an adequate amount of vitamin A.

The test is carried out in a dark room. The subject is asked to look into the machine and to state when he sees the middle dot on a screen in which the dots are arranged in the form of a quincunx. The five dots are of graded illumination, and their brightness is controlled by a rheostat. This rheostat is connected with a dial, the divisions of which represent the logarithms of the intensity of light expressed as "milli-

1:905-907 (April 16) 1938. Booher, L. E.: Vitamin A Requirements and Practical Recommendations for Vitamin A Intake, J. A. M. A. **110**:1920-1925 (June 4) 1938. Booher, L. E., and Williams, D. E.: A Study of the Biophotometer as a Means of Measuring the Vitamin A Status of Human Beings, J. Nutrition **16**: 343-354 (Oct.) 1938.

5. (*a*) Palmer, C. E., and Blumberg, H. E.: The Use of Dark Adaptation Technique in the Measurement of Vitamin A Deficiency in Children, Pub. Health Rep. **52**:1403-1419 (Oct. 8) 1937. (*b*) Palmer, C. E.: The Dark Adaptation Test for Vitamin A, Am. J. Pub. Health **28**:309-319 (March) 1938. (*c*) Snelling, C. E.: The Biophotometer as a Test for Vitamin A Deficiency, J. Pediat. **13**: 506-509 (Oct.) 1938. (*d*) Isaacs, B.; Junge, F. T., and Ivy, A. C.: Vitamin A Deficiency and Dark Adaptation, J. A. M. A. **111**:777-780 (Aug. 27) 1938.

foot-candles." Thus, in each reading taken the amount of light required by the subject to see the middle dot of the quincunx is recorded.

The testing period of twenty-three minutes is divided into three parts: (1) a ten minute period in the dark, during which readings are taken to familiarize the subject with the testing procedure (the fore-period); (2) a three minute exposure of the subjects' eyes to a bright light for the purpose of bleaching the visual purple (the bleaching period), and (3) a second ten minute period in the dark, during which visual purple is regenerated (the recovery period). During the recovery period four readings are taken at three minute intervals, the first of which is taken approximately twenty-five seconds after the bleaching light has been turned off. In interpreting the findings Jeans stated that the shape of the curve for the entire test should be considered but indicated that the two most significant readings are (1) the one taken immediately after the light is turned off and (2) the one at the end of the test.

In the present study a standard procedure was used in testing. All of the timing for the test was done with a stop watch. Special care was taken to expose the subject's eyes to the bright light for exactly three minutes and to insure that he kept his eyes open and looked directly at the light during the bleaching period. In analyzing the data the two readings indicated by Jeans as most significant were used, namely, the one taken immediately after the bleaching period and the last one in the test. For the sake of brevity these will be referred to hereafter as the "first" and "last" readings. To avoid confusion the entire series of eight readings taken during the twenty-three minute period will be termed a "test," the individual observations being designated as "readings."

The data obtained are reported in dial readings rather than in "milli-foot-candles" of light. The reasons for this were explained fully by both Palmer [5a] and Isaacs [5d] and will not be reviewed here. In order to facilitate comparison with the standards suggested by Jeans and his co-workers and with the work of other laboratories, the "milli-foot-candle" equivalents for some of the dial spaces of the instrument used, as furnished by the manufacturers of the biophotometer, are given in table 1. The limits of the normal, borderline and subnormal zones suggested by Jeans are also included.

RELIABILITY OF THE BIOPHOTOMETER TEST

The first step in attacking any problem of research is to determine the reliability of the test to be used for measuring results, that is, the degree to which the findings can be reproduced by the same operator on the same subjects under standard conditions. In the case of the Birch-Hirschfeld photometer, work never proceeded beyond this stage,

because of inability to secure reliable readings. In the present study the data used in determining the reliability of the biophotometer test were obtained from 6 adults who were given from sixteen to twenty tests each, 50 children given six tests each and 283 subjects—48 adults and 235 children—who were given two or three tests each. Space does not permit presentation of the details of the methods used, but the essential findings may be summarized as follows:

1. The readings for individual subjects vary considerably from test to test even under standard conditions. This variation may be sufficient to change the classification of the subject from the normal to the borderline or the subnormal zone (by the Jeans standards) or the reverse. It is obvious, therefore, that single tests of a subject are of no value for diagnostic purposes.

TABLE 1.—*Milli-Foot-Candles of Light Equivalent to the Dial Spaces for the Biophotometer Used in This Study*

Dial Spaces	"Millifoot-Candles"	Zone Represented by First Reading in Recovery Period	Dial Spaces	"Millifoot-Candles"	Zone Represented by Last Reading in Recovery Period
5	3.41	Subnormal	40	0.136	Subnormal
10	2.15	Subnormal	43	0.103	Upper limit of subnormal
15	1.36	Subnormal	45	0.0855	Borderline
18	1.03	Upper limit of subnormal	50	0.054	Upper limit of borderline
20	0.855	Borderline	55	0.034	Normal
23	0.650	Upper limit of borderline	60	0.0215	Normal
25	0.540	Normal	65	0.0136	Normal
30	0.341	Normal	70	0.0085	Normal

2. The first test of a child is the least reliable single test as judged by the self-correlation technic. The second test, however, is as reliable as any of the subsequent single tests. It is suggested, therefore, that in working with children the first test should be considered only a practice test.

3. Although the results of individual tests vary, the direction is as often up as down, so that the trend for an individual subject is fairly uniform. The test may be considered fairly reliable, therefore, if the trend of a subject's readings over an appreciable period is used both for establishing a base line in the control period and for determining the level with an experimental regimen.

4. The mean readings in repeated tests of groups of subjects are fairly stable; they show no consistent tendency either to improve or to regress on successive tests. This is due to the fact that the random variations of individual subjects tend to balance each other in the total group. Thus, the learning factor reported by Palmer was not observed

in this study. It follows, therefore, that the effect of an experimental procedure may be measured by the change in mean readings, provided (*a*) that large enough groups are used, (*b*) that the study is adequately controlled and (*c*) that the significance of the differences obtained is determined by accepted procedures.

5. A study of other factors that might affect the test showed that the time of the day the test was taken, the time in relation to meals and the operator giving the test had no significant effect on the readings obtained. The age of the subject, however, did have an appreciable effect on biophotometer readings. Adults over 30 years of age with an optimal intake of vitamin A had significantly poorer dark adaptation than did children or young adults. If, therefore, the test is to be used, different standards should be used for older subjects.

This preliminary work demonstrated that the biophotometer test is only fairly reliable and that its use should be safeguarded by the aforementioned considerations.

VALIDITY OF THE BIOPHOTOMETER TEST AS A MEASURE OF VITAMIN A STORES

The degree to which the test can be duplicated under standard conditions having been determined, the crucial problem of its validity can be considered; that is, whether the results of the test are in reality an index of the subject's nutritional status in respect to vitamin A. This problem was subjected to three types of attack: (1) a comparison of the biophotometer readings of subjects from high and of those from low socioeconomic groups: (2) the effect of vitamin A supplementation on the readings of subjects with low levels of the vitamin as compared with those of a matched group and (3) the effect of a long period of depletion of vitamin A and subsequent supplementation on the biophotometer readings.

COMPARISON OF BIOPHOTOMETER READINGS OF SUBJECTS OF HIGH AND THOSE OF LOW SOCIOECONOMIC STATUS

If the biophotometer test is a valid measure of vitamin A stores there should be a significant difference in the readings for subjects with good and those with poor dietary histories. To check this point, two groups of children representing the two extremes of socioeconomic status were compared (100 children from the University Laboratory School and 160 children from two of the poorest sections of the city). Comparisons were made on two bases: (1) the mean biophotometer readings for the groups and (2) the percentage of children in each group whose readings classed them as normal, borderline and subnormal. It

is seen in tables 2 and 3 that by both methods of comparison the children from the better socioeconomic group had a definitely higher status than those from the less favored groups. The mean biophotometer readings for the 100 children from the laboratory school were 22.8 dial spaces for the first and 62.6 for the last reading in the recovery period; those for the 160 children in the poorer group, 19.7 and 55.8 respectively for the same readings. The differences between these readings for the two groups were eight times the probable error and therefore are statistically significant. By the second method of analysis, moreover (table 3), it was seen that 26 per cent of the university group were classed as "normal" by the Jeans standards and only 21 per cent as definitely sub-

TABLE 2.—*Means and Standard Deviations of the First and Last Readings in the Recovery Period of Children from a High and a Low Socioeconomic Group*

Classification of Subjects	Number of Subjects	First Reading in Recovery Period		Last Reading in Recovery Period	
		Mean Dial Reading	Standard Deviation	Mean Dial Reading	Standard Deviation
High socioeconomic group.....	100	22.8	4.21	62.6	10.21
Low socioeconomic group.....	160	19.7	4.43	55.8	8.65

TABLE 3.—*Percentage of Children from the High and Low Socioeconomic Group Classified as Normal, Borderline or Subnormal According to the Jeans Standard*

Subjects	Number	Normal, Percentage	Borderline, Percentage	Subnormal, Percentage
High socioeconomic group.....	100	26.0	53.0	21.0
Low socioeconomic group.....	160	15.6	41.9	42.5

normal, as compared with 15.6 per cent of the poorer group who fell in the "normal" and 42 per cent in the "subnormal" zone.

These comparisons tend to support the validity of the test, since the group that presumably had the better stores of vitamin A also gave the higher biophotometer readings. Acceptance of validity on this basis, however, makes it necessary to explain the fact that 74 per cent of the superior group fell in the borderline and subnormal zones. It is recognized, of course, that the diets in this group may not all have been optimal in vitamin A, but it is difficult to believe that so large a number were deficient. An alternative explanation would be that the diets of the majority of these children were in reality adequate and that the standards of Jeans are too high. This possibility is supported by the finding that the mean readings for the 46 children in the university group who had been taking vitamin A concentrates were no higher than those for the rest of the group.

EFFECT OF A VITAMIN A SUPPLEMENT ON BIOPHOTOMETER READINGS

The second approach was to determine whether subjects with subnormal readings could be made to improve by a vitamin A supplement. The children from the poorer locality were used to check this point. From the original 160 children who were given tests, two groups of 50 each were formed by pairing children on the basis of age, height, weight, intelligence quotient and original biophotometer readings. Although individual pairs could not be perfectly matched on every item, care was taken not to match a child who was much underweight with one over average or one with a low intelligence quotient with one with a high quotient and to give the odds on the different items first to one group and then to the other. As a result, two groups were formed whose means for every item used in matching were almost identical and whose individual pairs were remarkably alike in significant factors. These groups were considered well adapted for the study.

After a second test, therefore, each child in the experimental group was given a supplement of vitamin A in the form of carotene for five days a week during a period of eight weeks.[6] For the first six weeks this daily supplement was 10,000 units; during the last two weeks it was increased to 20,000 units per day. Each child was given his capsule of carotene individually and was required to swallow it in the presence of the observer. At two week intervals biophotometer tests were given all the children in both the control and the experimental groups, making a total of six tests of each child. It should be noted that this study differs from those reported in the literature in the size of the group studied and in the facts that the controls and the experimental subjects were carefully matched at the beginning of the investigation and the progress of each child was observed by regular tests throughout the study.

The effect of the supplement was judged by comparing the progress made by the two groups on the basis of: (1) the mean readings, (2) the percentage of children in normal and subnormal zones and (3) the relative improvement made by partners in the matched pairs.

Mean Biophotometer Readings.—When the mean biophotometer readings for the two groups in each of the six tests are compared (table 4; chart 1) it is seen that there was little difference in their progress. The experimental group did, it is true, show a net increase in the mean readings of 1.5 dial spaces for the first reading in the recovery period, while the control group showed a decrease of 0.8 dial spaces. When, however, the trend for the means of the individual tests is observed (chart 1), it is seen that this difference was contributed

6. The carotene was supplied by the S. M. A. Corporation, Cleveland.

largely by the last two tests and may easily have been fortuitous. The same trend was noticed in the last readings in the recovery period; the experimental group was slightly in the lead but not significantly so. If, however, each of the two groups is subdivided into the subjects for whom the highest, the intermediate and the lowest original test values were recorded, it is found that most of the improvement was made by the group for which the levels were lowest. The means for the first reading for the 16 controls and the 16 experimental subjects in this lowest group, identical at the beginning, diverged widely on succeeding tests and were 4 dial spaces apart on the sixth test (chart 1). That this improvement of subjects with low levels of vitamin A was not due to the "centripetal" drift observed by Isaacs and his associates [5d] is evidenced by the fact that the matched partners in the control group did not show a significant improvement.

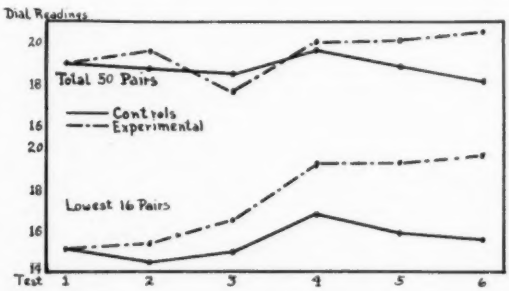

Chart 1.—Comparison of the mean readings for the control and for the experimental group in each test.

TABLE 4.—*Mean Dial Readings of Each Group of 50 Children in Each of the Six Tests*

	Total (50 Pairs)		Lowest (16 Pairs)		Middle (18 Pairs)		Highest (16 Pairs)	
	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental
First reading in recovery period								
First test	18.9	19.0	15.1	15.1	18.8	19.5	22.6	22.4
Second test	18.7	19.6	14.5	15.4	19.6	18.8	21.8	21.6
Third test	18.5	17.6	15.0	16.5	19.8	16.8	20.4	19.8
Fourth test	19.6	20.0	16.8	19.3	19.3	18.8	22.8	22.2
Fifth test	18.9	20.1	15.9	19.3	19.2	18.8	21.4	22.2
Sixth test	18.1	20.5	15.6	19.6	17.6	19.4	21.1	22.8
Last reading in recovery period								
First test	56.1	55.0	54.1	50.1	55.0	55.6	59.3	58.6
Second test	57.1	53.7	53.9	49.1	55.6	54.9	61.9	56.9
Third test	55.3	53.6	53.6	52.5	54.8	52.3	57.4	56.1
Fourth test	56.3	55.2	54.9	53.5	55.3	52.6	58.8	59.8
Fifth test	55.3	56.3	53.4	55.4	53.9	55.5	58.7	58.1
Sixth test	52.8	55.6	51.8	54.8	52.1	54.2	54.9	58.1

Change in Percentage of Children in Normal and in Subnormal Zones.—An advantage for the experimental group is also shown by the change in the number of subjects whose readings classed them as "normal" or "subnormal" by the Jeans standards at the beginning and end of the study (table 5). The percentage of normal subjects in the experimental group increased from 8 to 20, while in the control group it remained unchanged. Conversely, the percentage of the experimental subjects rated as definitely subnormal decreased from 50 to 32, while that of the control group increased from 44 to 56. It is again noted that the greatest part of the improvement was contributed by the 16 children for whom the lowest original readings were recorded.

TABLE 5.—*Percentage of Children in Each Group Classified as Normal, Borderline and Subnormal at the Beginning and End of the Study*

Group	Normal		Borderline		Subnormal	
	Control	Experimental	Control	Experimental	Control	Experimental
Total (50 pairs)						
Second test	8.0	8.0	48.0	42.0	44.0	50.0
Last test	8.0	20.0	36.0	48.0	56.0	32.0
Lowest (16 pairs)						
Second test	0.0	0.0	12.5	6.2	87.5	93.8
Last test	6.2	6.2	12.5	56.3	81.3	37.5
Middle (18 pairs)						
Second test	5.6	0.0	50.0	55.6	44.4	44.4
Last test	0.0	16.6	38.9	38.9	61.1	44.5
Highest (16 pairs)						
Second test	18.7	25.0	81.3	62.5	0.0	12.5
Last test	18.7	37.5	56.3	50.0	25.0	12.5

Relative Progress of Partners in Matched Groups.—The most severe as well as the most reliable method of assessing the results is to compare the relative progress of the individual partners in the 50 matched pairs. To facilitate such a comparison chart 2 has been prepared. It shows the first dial reading in the recovery period for each of the 50 matched pairs in each of the six tests. It is evident at a glance that there is great variability in the readings from test to test, with no pronounced indication of any superiority of the experimental group over the control. If individual charts are examined it is found that the status of 22 experimental subjects was improved, that of 11 was the same and that of 17 was actually lower than at the beginning; in the control group the status of 15 was improved, that of 7 was the same and that of 28 was worse than at the beginning. When the final status of the partners is compared, moreover, in 30 pairs, or 60 per cent, it is seen that the

experimental child had a somewhat higher reading than the control partner with whom he was matched at the beginning; in only 12 pairs, or 24 per cent, did the control child have the advantage. These evaluations, however, exaggerate the differences between the groups. From

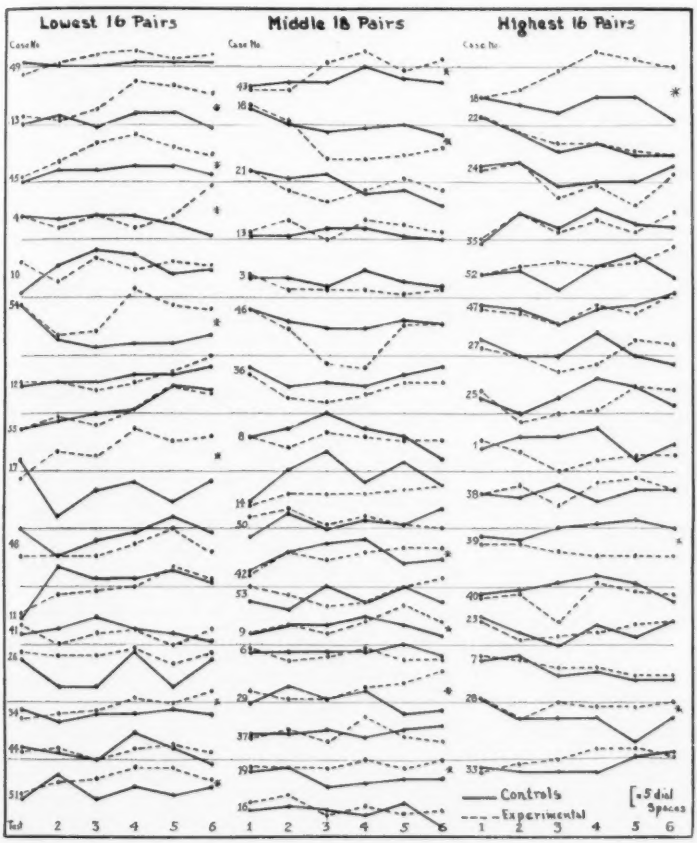

Chart 2.—Readings for each of the 50 pairs of children in each test.

actual inspection of the chart, only the ones marked with an asterisk seem to us to be real differences. There were only 16 such pairs, and in 14 of these the advantage was with the child to whom the supplement was given.

It is of special interest to note again that it was in the lowest group that the improvement was most marked. Of the 14 children showing

decidedly better progress than their controls, 7 were in this low group, 5 were in the middle group and 2 were in the highest group. This is in accord with the claims of Booher and others that the test is most useful for measuring progress in cases of marked dysadaptation. It should be pointed out, however, that 46 of the 50 experimental subjects were in the borderline or the subnormal zone at the beginning and should presumably have responded to the supplement if the test were a precise measure of vitamin A stores.

To sum up the results of this portion of the study, there appears to be little doubt that the supplement did cause some improvement. The experimental group showed a greater advance in mean dial reading, a somewhat greater increase in the percentage of children in the normal zone and more children whose gains exceeded those of their partners. The results were not sufficiently clearcut, however, to warrant the conclusion that a child's stores of vitamin A bear a direct relation to the biophotometer readings. This is shown by the facts that more than half the children receiving the supplement failed to improve and that 26 per cent of the control children gained more than their partners. It would seem, then, that while the test may be of some value in showing the relative progress of groups, its usefulness in determining the nutritional status for vitamin A of individual subjects is doubtful. Since, however, most of the improvement noted was made by the children for whom the test values were lowest, it may be concluded that a child with a test value in the very low zone is more apt to show subclinical vitamin A deficiency than one for whom a higher test value is recorded.

EFFECT OF A DEPLETION DIET ON BIOPHOTOMETER READINGS

The most crucial attack on the problem of the validity of the test was to study the effect of a diet low in vitamin A on the biophotometer readings to ascertain whether the results reported by Jeghers and by Booher for 1 subject each could be reproduced. Six women served as subjects. These subjects ate a constant weighed diet which as calculated contained less than 100 units of vitamin A per day. All subjects ate identical amounts by weight of any food which contained a significant amount of vitamin A or carotene, but certain foods, such as cakes made from hydrogenated fat, sugar, egg white and white flour, were allowed ad libitum. The plan was to continue the diet until the subjects were definitely night blind, as judged by the test, and then to determine the amount of a vitamin A supplement required to restore them to normal. Unfortunately this was not possible except in 2 cases, as the school year closed before this end was accomplished. Three subjects were on the depletion diet for twenty-five, thirty and forty-four days respectively,

and the remaining 3 were on this diet for one hundred and twenty-three days, having each received a small supplement, of 1,000 units, of vitamin A on the sixty-fifth day and again on the seventy-second and seventy-sixth day.

The individual biophotometer readings for the six subjects during these periods are shown in chart 3. It will be noted that only 2 of the

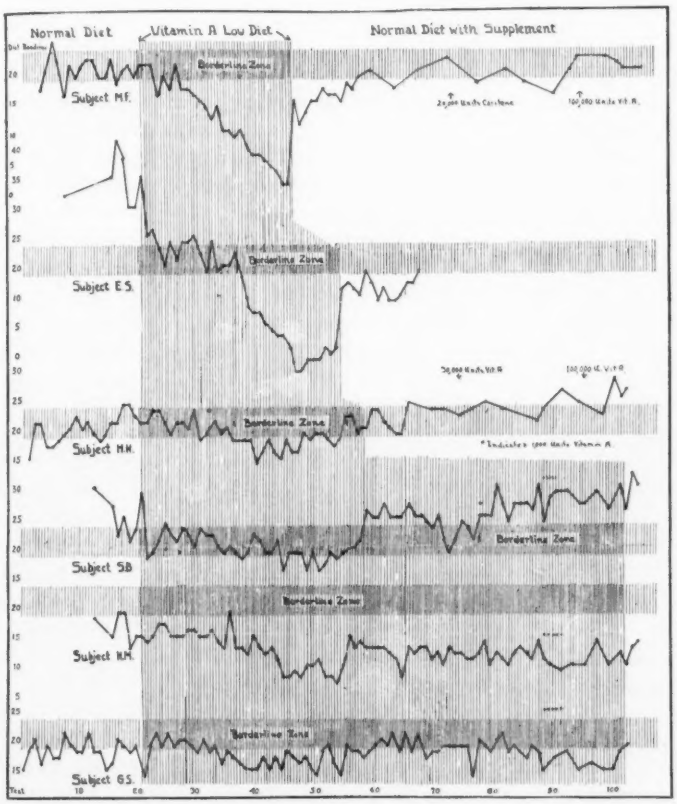

Chart 3.—Individual readings for the 6 subjects on the depletion diet.

6 subjects showed the expected drop in biophotometer reading. Both of these showed a significant change at the end of two weeks and dropped rapidly thereafter. M. F. at twenty-five days exhibited definitely impaired dark adaptation; in fact, the readings were as low as the instrument used would measure. She was then given 100,000 units

of vitamin A in the morning and tested at two hour intervals during the first day. Her response was prompt and spectacular; the readings were almost up to their original level by the end of the day. In the case of E. S. also the values dropped rapidly on the depletion diet from the original level of 35 to 5 at the end of forty-five days; they likewise rose immediately when she was given 2,000 units of vitamin A. Had only these 2 subjects been studied, conclusions as to the validity of the test would have seemed warranted. The other 4 subjects, however, did not exhibit this response, though 3 of them continued the experiment for four months. Their day to day readings showed much variation, with occasionally a small drop and then a rise suggestive of improvement. Unfortunately, however, these rises were not coincident with the periods of supplementation. In fact, one could not by inspection of the graphs of these 4 subjects determine which were periods of depletion and which periods when supplements were being employed.

The most obvious explanation for the variation in response of these 6 subjects is that there must have been a difference in their stores of vitamin A. A study of their dietary histories does not support this belief. Of the 2 subjects who showed decreased readings, 1 had a history of a low intake of vitamin A, but the second apparently had an exceptionally high intake. Of the 4 subjects who showed no significant change in readings during the period of depletion, 3 had dietary histories showing a very high intake of vitamin A, while the fourth had only a fair dietary history. Moreover, if the biophotometer test is a valid indication of the body's stores of vitamin A, the subjects for whom the lowest original readings were recorded should have been the ones to respond by decreased readings when placed on a diet deficient in vitamin A, but this was not the case. Two subjects whose original readings placed them in the borderline or the deficient zone (G. S. and K. M.) showed no significant drop after four months, and 1 subject (E. S.) whose readings went down rapidly with the depletion diet had the highest original readings of any in the group.

The most interesting case in the entire study was that of G. S., who had been given frequent tests with the biophotometer for nine months previous to the time she was placed on the deficient diet, so that a consecutive study of the readings for over a year was possible. When she was first tested, the readings classified her at the upper limit of the subnormal zone. Since an ophthalmologic examination revealed no cause for these low readings, an attempt was made to increase them by supplements of vitamin A. The dose varied from 20,000 to 100,000 units of vitamin A per day. Various supplements were used in turn; halibut liver oil, cod liver oil concentrate, cod liver oil and carotene. This subject was given a total of 157 biophotometer tests during one year. The first reading in the recovery period for all of her tests are

shown in chart 4. It will be noted that regardless of whether this subject received 100,000 units of vitamin A per day or less than 100 units there was no tendency for the general trend of the readings to vary. The mean for the 157 tests was 17.6 with a standard deviation of 1.7 for the first reading in the recovery period and 56.9 with a standard deviation of 4.6 for the last.

It is possible, of course, to explain the failure of this subject to respond to changes in her intake of vitamin A if it is assumed that the standards were too high and the capacity for storage of vitamin A of the same order as that found in experimental animals. If her adaptation was normal at the outset, increasing the vitamin A intake even up to 100,000 units would, of course, not effect any change. Furthermore, if a considerable proportion of the large excess of vitamin A ingested during the supplementation period was stored, it might easily

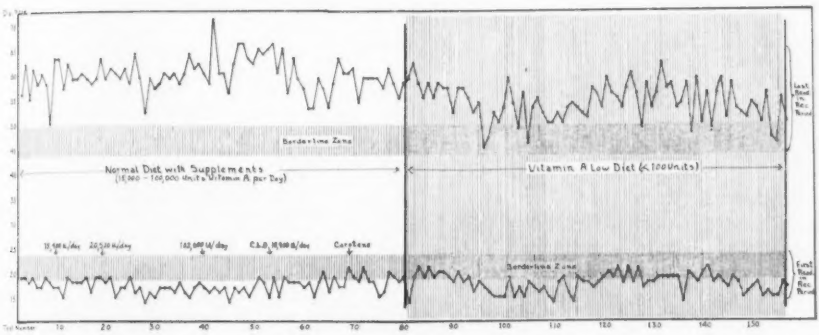

Chart 4.—First and last readings in the recovery period for the one hundred and fifty-seven tests given subject G. S.: The intake of vitamin A varied from 100,000 to 100 units per day.

have been sufficient to supply her during the four months of depletion. This would seem a plausible explanation. It is difficult, however, to reconcile it with the report of Jeghers on a subject who after large supplements of vitamin A showed lowered biophotometer readings within a week on a deficient diet.

The results in these 6 cases emphasize the dangers of drawing conclusions from findings on 1 or 2 subjects. The fact that 2 subjects showed decidedly lowered readings after twenty-five and forty-four days respectively on a deficient diet must be interpreted to mean that the results of the biophotometer test are influenced by the vitamin A intake of some persons. On the other hand, the facts that 4 subjects failed to respond after four months on the depletion diet and that the response of the 6 subjects was not consistent with either their original

biophotometer readings or their dietary histories indicate that the relation between the test and the vitamin A stores is certainly not clearcut and infallible.

COMMENT

The evidence presented shows clearly that there is some relation between biophotometer readings and vitamin A stores. Three lines of evidence support this contention: 1. The mean readings of children in the higher socioeconomic group were significantly higher than those in the lower socioeconomic group. 2. The children who were given a supplement showed a slight improvement over their matched controls. 3. Two subjects on a diet low in vitamin A responded with lowered readings and immediately improved when a supplement was given.

While this evidence is in support of the validity of the test, it does not warrant the contention that the test can be used as a diagnostic measure for determining deficiency in vitamin A, nor does it signify that changes in readings are necessarily associated with changes in vitamin A stores. The following evidence makes such conclusions unwarranted: 1. Many subjects known to be living on a diet rich in vitamin A were classified by the readings as subnormal. 2. The majority of the children who were given a supplement never attained "normal" readings. 3. The relation of vitamin A to biophotometer readings was not consistent, in that 30 per cent of the children in the control group who gave original low readings improved without any supplement while 56 per cent of the experimental group who received one did not. 4. Four out of 6 subjects did not respond to a diet low in vitamin A with lowered readings. 5. There was considerable variation in readings for the same subject on successive tests. Thus many subjects tested under standard conditions were classified as normal on one test and borderline or even subnormal on the next.

Part of this negative evidence is removed if one admits that the suggested standards are too high. Such an admission carries with it the necessity of recognizing that the incidence of mild vitamin A deficiency is much lower than has been reported. Moreover, even with lower standards for normal readings there would be some subjects giving low readings who had normal stores and some giving higher readings who had poor stores. The question of the value of the biophotometer test, then, is dependent on the purpose for which the test is used and the interpretation given to the results. It has been shown that the means of the biophotometer readings for large groups of subjects remain fairly constant from test to test and consequently could be used to place the groups in relation to each other. In well controlled studies the test could also be used to measure the effect of a supplement by noting the effect on the mean for the group. When, however, the individual subject is considered, the test is much less useful.

It does not serve satisfactorily for diagnosing mild vitamin A deficiency. It is true that a subject who gives very low readings is more apt to be deficient than one who gives high readings, but a change in any one subject's readings from test to test is as apt to be due to chance as it is to be related to his nutritional status for vitamin A. The procedure recommended is that of testing persons frequently and judging the effect of a supplement by comparing their progress with that of well matched controls. This method is, however, expensive of time and is warranted only when there is no better means available for measuring vitamin A deficiency. The situation is similar to the use of capillary fragility in measuring vitamin C deficiency. In a well controlled study, until better methods are available, both tests might be advantageously used, together with other measures of nutritional status, to follow the progress of a group, but the interpretation of results for individual subjects should be made with caution.

It should be emphasized that these conclusions are concerned not with the fundamental problem of whether tests of dark adaptation can be used to determine vitamin A stores but merely with the usefulness of the biophotometer for this purpose. It is recognized that some of the difficulties encountered are mechanical ones which presumably could be remedied in the construction of the instrument used. All tests which depend on the subject's stating when he sees a point of light, however, carry a subjective element, and errors of interpretation are apt to occur unless the reliability of the test is determined and the study carefully controlled.

Certainly the theory behind the test is sound, and the results even with an instrument as simple in construction as the biophotometer, are sufficiently encouraging to warrant further study both for improving the instrument for measuring dark adaptation and for determining its validity as a measure of nutritional status for vitamin A. Whatever may be the outcome, great credit is due to Jeans and his co-workers and to the makers of the biophotometer for taking the initial step in this new line of nutritional research.

SUMMARY

The results of over 2,000 biophotometer tests on 459 persons were analyzed to determine the reliability of the test and its validity as a measure of the nutritional status for vitamin A. The outstanding findings follow.

1. Single tests of a subject are unreliable, as the readings may vary so widely on successive tests, even with a constant dietary regimen, as to change his classification to or from the normal or the subnormal zone. The general trend, however, of the readings for the same subject is fairly constant, and the test, therefore, can be used to determine the

level for a person or for a group if a sufficient number of readings are obtained to determine their variability. This procedure is time consuming and practically rules out the test, even if it were valid, for routine clinical use.

2. For children from a high socioeconomic level the biophotometer readings were significantly higher than for children from a low socioeconomic level. Only 26 per cent of the children in the superior group, however, gave readings which classified them as "normal" according to the Jeans standards.

3. A supplement given to 50 children for whom the original readings were low caused no significant difference in the mean readings of the group as a whole as compared with those of a matched group of 50 controls. More than half of the children receiving the supplement, moreover, failed to improve, and 26 per cent of the control children gained more than did their partners. It is worthy of note, however, that in 14 of the 16 pairs in which a real difference was evident the odds were in favor of the child who received the supplement.

4. A depletion diet caused a significant change in the biophotometer readings for only 2 of 6 subjects, although 3 of the others remained on the diet for four months. The response of the 6 subjects to the depletion diet was not consistent with either their original biophotometer readings or their dietary histories.

These results make it evident that, although some relation exists between the biophotometer readings and vitamin A nutrition, the relation is not close enough to warrant the use of the test as a means of diagnosing subclinical vitamin A deficiency. The basis idea, however, of the use of measurements of dark adaptation for determining deficiencies of vitamin A seems promising and worthy of further experimentation.

Hazel Lapp, Berniece Anderson and Helen Parks gave technical assistance in this study, performing many of the tests. Helen Heinzelman collaborated in the section on the effect of a depletion diet on biophotometer readings. Miss Heinzelman carried out the work on 2 subjects and has reported the details in her Master's thesis, "The Relation of Vitamin A Intake to Visual Adaptation to Light and Dark as Determined by the Biophotometer," University of Chicago, 1939.

INFANTILISM IN ULCERATIVE COLITIS

SIDNEY DAVIDSON, M.D.
Resident in Medicine
NEW YORK

Infantilism has been frequently seen as a sequela of such chronic debilitating diseases as chronic renal disease,[1] congenital and rheumatic heart disease, diabetes mellitus, avitaminosis, congenital syphilis, Addison's disease,[2] Still's disease [3] and congenital hemolytic icterus.[4] Infantilism has been frequently reported in gastrointestinal disorders, especially in celiac disease and idiopathic steatorrhea.[5] In one series of 15 cases of idiopathic steatorrhea, characteristic stigmas of infantilism appeared in 10.[5a] It has been found also in cases of chronic intestinal tuberculosis.[2] I have seen 1 such case in the past year.

Despite the frequent mention of infantilism associated with the gastrointestinal disorders mentioned, it has not been reported in ulcerative colitis. Bargen,[6] in summarizing the sequelae in 1,500 cases of ulcerative colitis, did not mention infantilism, nor did he, Jackman and Kerr [7] speak of it in discussing another series of 871 cases, in 243 of which the patients were in the second and third decades of life. Mackie,[8] in his report on the deficiency states in 75 cases of ulcerative colitis, did not mention infantilism, nor did Lups [9] or Rankin, Bargen

From the Medical Service of Dr. L. Lichtwitz, Montefiore Hospital.

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and Buie [10] in their detailed discussion of the disease. It probably has been seen but not reported.

In the past two years at Montefiore Hospital infantilism has been observed in 3 cases of ulcerative colitis.

REPORT OF CASES [11]

CASE 1.—L. E., a 17 year old white youth, was admitted to the private pavilion on Aug. 17, 1937. His history was uneventful until 1932, when, at the age of 12 years, he was operated on for a rectal abscess and fistula. He lost considerable weight and during his slow convalescence began to have diarrhea, which continued intermittently until 1936. At this time failure of physical development was noted, and he was given anterior pituitary extract parenterally. There was some improvement of the gastrointestinal symptoms and a gain in weight. Soon after he began to have severe cramps and fever in addition to the diarrhea and on admission was having eight bowel movements a day.

Physical Examination.—The patient was afebrile, emaciated and poorly developed, appearing about 12 years of age rather than his stated age of 17. The heart, lungs and abdomen appeared normal on physical examination. The blood pressure was 90 systolic and 50 diastolic. There was no pubic, axillary or facial hair. The penis was infantile; the right testis, small but descended. The left testis was not palpable in the scrotum or inguinal canal. He weighed 50 pounds (22.7 Kg.).

Laboratory Data.—The hemoglobin content was about 4.5 Gm. except for temporary remissions after blood transfusions. The stools were liquid and brown and contained gross blood and mucus. Studies of fat in dry stools showed 7.2 per cent total fat, with 3.5 per cent fatty acids and 3.7 per cent neutral fat.

Course.—He was treated with a high vitamin diet, vitamin C, gonadotropic substance from the urine of pregnant women, liver extract given intramuscularly and a series of transfusions. Little improvement resulted. Bilateral parotitis, gangrenous stomatitis and bronchopneumonia developed, and he died on Sept. 10, 1937.

Postmortem Examination.[12]—Bilateral bronchopneumonia, bilateral parotitis, gangrenous stomatitis, gingivitis and esophagitis were observed. There were old infarcts of the spleen and evidences of old rheumatic infection of the mitral valve. The gastrointestinal tract revealed an edematous intestinal mucosa, with extensive confluent ulceration of the entire ileum and colon. The glomerular and reticular layers of the adrenal cortex were intact, but there were degenerative changes in the fascicular layers. There was marked hypoplasia of the tubules of the testes, with virtually no cellular differentiation. Spermatogenesis was absent. The interstitial cells had large vesicular nuclei with clear cytoplasm.

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10. Rankin, F. W.; Bargen, J. A., and Buie, L. A.: The Colon, Rectum and Anus, Philadelphia, W. B. Saunders Company, 1932.

11. Case 1 was a private case of Dr. L. Lichtwitz; cases 2 and 3 were from the gastrointestinal division of Dr. J. L. Kantor.

12. Postmortem examination in case 1 was done by Dr. William Sternberg; in case 2, by Dr. David Silberman. The special studies of the pituitary were made by Dr. Charles Spark.

CASE 2.—R. H., a white boy 15 years of age, was admitted to the medical service in 1936 because of bloody diarrhea. In infancy he had had eczema; at the age of 9 years, typhoid fever. Between the ages of 10 and 12 years he had developed normally but was always small of stature. In 1934, at the age of 13, he began to have attacks of bloody diarrhea and abdominal cramps. He was hospitalized with some improvement but had an exacerbation with recurrence of abdominal complaints in 1936, when he was again hospitalized. At that time, at the age of 15, he was noted to be physically immature, and the diagnosis of secondary infantilism was made. He was treated with antidysenteric serum without results and then transferred to Montefiore Hospital.

Physical Examination.—The patient was undernourished and underdeveloped and seemed much younger than his stated age of 15. He weighed 63 pounds (28.6 Kg.) and was 59 inches tall (149.9 cm.). There was no hair on the face, axillas or pubis. The heart was normal; the lungs were clear. Neither liver nor spleen was palpable, nor were there other abdominal masses.

Laboratory Data.—Analyses of the urine showed some albumin and an occasional cast. The hemoglobin content was 80 per cent on admission but soon dropped to 60 per cent, at which it remained. The urea nitrogen content of the blood was 7.1 mg. per hundred cubic centimeters and the dextrose content 84 mg. The serum proteins were 5.8 Gm. per hundred cubic centimeters with 3.2 Gm. of albumin and 2.6 Gm. of globulin. The stools constantly contained gross or occult blood. Roentgen studies of the gastrointestinal tract were interpreted as typical of colitis gravis of the entire colon.

Course.—After one year's supportive therapy, the patient was discharged unimproved in May 1937. He did well for a while, but his general condition became worse, although he had but three or four bowel movements daily. He was readmitted in June 1938.

Readmission.—On admission he weighed but 51 pounds (23.1 Kg.), 12 pounds (5.4 Kg.) less than he had weighed on the previous admission two years before. His height was the same; he was pale and emaciated, and his apparent age was 12 years. His voice was high pitched. There was no hair on the face, pubis or axillas. The heart and lungs appeared normal on physical examination. The liver was enlarged down to the umbilicus, and the spleen was palpable. The skin was dry and hardened. The penis was small and atrophic. The testes were small and soft.

Laboratory Data.—The hemoglobin content was 36 per cent, with 2,600,000 erythrocytes. The serum proteins were 6.5 Gm. per hundred cubic centimeters, with 2.1 Gm. of albumin and 4.4 Gm. of globulin. The urea nitrogen content of the blood was 6.2 mg. per hundred cubic centimeters, the calcium content 8.7 mg. and the phosphorus content 3.7 mg. The dextrose tolerance test with 30 Gm. of dextrose showed a fasting blood sugar content of 90, with a peak of 120 in one hour. There was no blood in the stool. Roentgen and fluoroscopic studies revealed pronounced enlargement of the transverse and descending aorta compared with the films made on previous admission. Roentgenograms of the skull and long bones demonstrated some osteoporotic changes. The congo red test showed 100 per cent retention of the dye in the tissues after one hour, indicating amyloidosis.

Course.—The patient was fed a high protein diet and given vitamin preparations, iron and liver by mouth. Nevertheless, he declined steadily and on Oct. 21, 1938, died, after three days of continuous blood diarrhea.

Postmortem Examination.—The heart weighed 100 Gm. There were no gross or microscopic abnormalities. The supravalvular portion of the aorta showed a

saccular dilatation, with a ring of narrowing. The descending portion of the thoracic aorta showed fusiform dilatation and at the level of the diaphragm appeared to be narrowed by a definite band of intima. Microscopically there was extensive destruction of the inner and outer elastic membranes and muscle fibers of the media of the aorta. The endothelial lining was fairly well preserved. In the outer layer of the adventitia were numerous large collections of chronic inflammatory cells with areas of hyalinization. The intimal coat had a similar appearance.

The gastrointestinal tract revealed a normal esophagus. The jejunal mucosa was slightly injected. The ileum displayed several patches with atrophic gray mucosa. The distal 12 inches (30.5 cm.) of the ileum and the entire colon showed a pink-tinged mucosa with pinpoint hemorrhages. There were several areas, especially in the sigmoid, where the mucosa was atrophic and gray. Otherwise the mucosa appeared hypertrophic and in numerous areas formed what appeared to be sessile papillae. Microscopically the mucosa and submucosa of the disal half of the ileum and the entire colon were extensively infiltrated with lymphocytes, plasma cells and a few eosinophils. The muscular coat was thickened and invaded by lymphocytes and plasma cells. The outer muscular coat showed nuclear shrinkage surrounded by a clear zone and honeycombed appearance. There were patches of amyloid beneath the epithelium in the small and large intestine.

The liver and spleen were both enlarged and contained considerable amyloid deposits. There was also amyloidosis of the kidney, with many glomeruli partly or completely replaced by amyloid. The pancreas was grossly normal but microscopically showed deposition of amyloid.

The parathyroids were enlarged, with moderate and marked replacement of the cells with amyloid. The thyroid was small; the follicles, large and filled with layered pink colloid. The adrenals were normal in size and showed fatty infiltration in all zones. There was marked amyloid replacement of the fascicular zone. Only a few pigmented cells remained. There was fibrosis of the medulla.

The testes were small and microscopically prepubertal. The tubules were small. There were no mitotic figures or any evidence of maturation. The interstitial cells were swollen, with round vesicular nuclei and colorless cytoplasm.

Because the literature contains no previous extensive pituitary studies in cases of secondary infantilism, the studies of the gland in this case are reported in detail:

The gland weighed 360 mg. It was sectioned in five sagittal levels. The sections were stained in Mallory's triple stain preceded by hematoxylin.

The most striking change in the anterior lobe was that seen in the nuclear elements of all the cells. All the nuclei were large and vesicular and many possessed large nucleoli. There was a definite increase in the number of basophil cells and a decrease in the number of acidophils. The basophil cells were large and had abundant deep-staining granules and showed little vacuolization. There were many small nodules of adenomatoid hyperplasia of the basophilic elements. There were scattered small foci of transitional basophils that were growing in the form of a syncytium. There were no colloid basophils.

The acidophil cells were most numerous in the region of the pars intermedia, and there their arrangement was rather atypical. The cells showed marked variation in size and shape and in places seemed to be growing in irregular anastomosing strands instead of the usual growth in cell columns and follicles. Many pyknotic nuclei were present in these atypical areas.

There were many "large chromaphobe cells." These had large vesicular nuclei and abundant watery cytoplasm containing scattered grayish granules which did not take either the acid or the basic stain. Many of these cells were arranged in follicles with retention of colloid droplets in the center, and both types of chromophil cells were intermingled among them.

A striking feature of the anterior lobe was the presence of large numbers of follicles containing colloid, and in some instances the colloid appeared to be calcified. A small proportion of the basophil cells were extremely bizarre, some reaching a giant size with abundant granules. Many binucleated cells were present.

The capillary bed of the anterior lobe appeared to be compressed by the hyperplastic growth of the cellular elements. There were few typical chromophobe cells. In many areas the nuclei of all the cell types were so closely aggregated that the growth appeared to resemble a syncytium. The residual lumen was present, and it was filled with colloid.

There was only an occasional basophil cell infiltrating the posterior lobe. Few pigmented pituicytes were present in the posterior lobe.

CASE 3.—H. F., a white youth aged 17, was admitted to the medical service in January 1938, because of bloody diarrhea. Until the age of 11 he had been a normal boy, with normal development and stature. In 1931 there was a sudden onset of fever, with pains in the joints and purpura. These symptoms lasted several months, at the end of which bloody diarrhea developed, for which he was hospitalized. There were exacerbations and remissions. In 1935, after a particularly severe bout, he was again hospitalized, and roentgen studies suggested the diagnosis of ulcerative colitis. After therapy with vaccines was ineffectual, ileostomy was done in 1936, followed by resection of half of the colon. There was no marked improvement, however, and he entered Montefiore Hospital complaining of weakness, anorexia and diarrhea, with six to ten black stools daily.

Physical Examination.—The patient was markedly emaciated, undernourished and underdeveloped, seeming not more than 12 years of age, despite the stated age of 17. He spoke in a childish, high-pitched voice. The face, axillas and pubis were devoid of hair. There was marked gingivitis and pyorrhea. The teeth were poor and carious, and the gums were red and bled readily. There was an ileostomy in the midline. The penis was small, as were the testes, which were palpable at the external inguinal rings. The fingers and toes were clubbed.

Laboratory Data.—There was a flattening of the dextrose tolerance curve, with a fasting sugar content of 70 mg. per hundred cubic centimeters and a peak of 103 in one hour. Gastric analysis showed free acid only after administration of histamine. The urea content of the blood was but 4.9 mg. per hundred cubic centimeters. The hemoglobin content was 56 per cent, with 3,600,000 erythrocytes. Roentgen studies of the gastrointestinal tract revealed the ileosigmoidostomy with resection of the colon down to the iliac portion. Proctoscopic examination revealed hemorrhagic proctitis.

Course.—Therapy consisting of diet, iron, vitamin C and liver was attempted. The hemoglobin content increased to 65 per cent; the weight to 74 pounds, and the patient was discharged in September 1938, somewhat improved, with the diagnosis of ulcerative colitis.

COMMENT

Infantilism in chronic disease is characterized by retardation or absence of sexual development, usually accompanied by diminished

growth. Although usually considered secondary to the underlying debilitating condition, both disorders in some cases have been considered to be due to a primary disease of the pituitary-hypothalamic complex. Chown and Lee,[13] in a careful study of a case of renal dwarfism, stated that both the renal disease and the endocrinopathy were due to a lesion in the pituitary-hypothalamic complex, with encephalitis as the probable etiologic agent. Gibson and Fowler,[14] reporting 8 cases of infantilism associated with diabetes mellitus, noted that the onset of the disease occurred in all cases after the cessation of development and suggested that the diabetes was not the cause of the infantilism but that both were due to a central lesion.

For the most part, however, infantilism in chronic disease is considered secondary and has been demonstrated, in some few cases, to be reversible. Apert [2] reported the case of a 17 year old diabetic patient who, treated before the insulin era, displayed marked physical and sexual immaturity. Insulin became available, and within one year of its use normal physical and sexual maturity was attained. Langston [4] cited the case of a 17 year old boy with congenital hemolytic icterus, whose development was that of an 11 year old child. After removal of the spleen and the use of anterior pituitary extract, he rapidly reached normal physical development.

Secondary infantilism in the chronic diarrheas is almost entirely due to the effects of the diarrhea, depriving the growing organism of an adequate supply of the substances needed for normal maintenance, maturation and growth. The faulty absorption from the gastrointestinal tract in such diseases creates not only a caloric deficiency but also deficiencies of nitrogen, vitamins and minerals. The need of the growing organism for these substances is greater during the period of maturation and, as was pointed out by Sherman,[15] is so urgent that a shortage of any essential factor becomes more quickly and strikingly apparent and is likely to be more harmful than in the case of the maintenance metabolism of the adult. It is not surprising, then, that infantilism occurs most strikingly in patients who are ill during the period of physical and sexual maturation. This was true in my cases and in the cases of steatorrhea described by Thaysen,[16] by Hanes and McBryde [5c] and by Bennett, Hunter and Vaughn.[5a]

13. Chown, B., and Lee, M.: Renal Rickets and Dwarfism as a Pituitary Disease, Am. J. Dis. Child. **53**:117 (Jan., pt. 1) 1937.

14. Gibson, R. B., and Fowler, W. M.: Infantilism and Diabetes Mellitus: Report of Eight Cases, Arch. Int. Med. **57**:695 (April) 1936.

15. Sherman, H. C.: Chemistry of Food and Nutrition, New York, The Macmillan Company, 1938.

16. Thaysen, T. E. H.: Idiopathic Steatorrhea. London. Oxford University Press, 1931.

Of all deficiencies, the most important is probably that of available calories. The interference with adequate absorption from the gastrointestinal tract by chronic diarrhea deprives the growing organism of an adequate supply of energy. Such caloric insufficiency in other states of malnutrition has been found both clinically [17] and experimentally [18] to have marked effects on maturation and growth. Stefko [17] in his studies on malnutrition found cryptorchism frequent in adolescent boys. Puberty was greatly retarded, and the external genitalia in general remained poorly developed. Microscopically the testes were prepubertal in appearance. The pituitaries of such boys seemed unaffected except for slight basophil hyperplasia.

In addition to caloric inadequacy deficiencies of nitrogen, vitamins and minerals play an important role in producing infantilism in the chronc diarrheas. In ulcerative colitis Welch and his co-workers [19] have demonstrated a negative nitrogen balance, which is increased during the more active stages of the disease. The need of the growing organism for nitrogen is great, and an inadequate supply, especially of the essential amino acids, can raise havoc with processes of growth.[20]

Specific vitamin deficiencies are frequently present in both ulcerative colitis [21] and steatorrhea.[22] Their effect experimentally, especially on the endocrine glands, is profound, and clinically they must play an important role in the disturbance of growth and endocrine balance seen in chronic diarrheas.

Experimentally, lack of vitamin A, riboflavin and vitamins D and E all have been shown to have a profound influence on the growth of animals.[23] Deficiency of vitamins A, B_1 and E have specific effects on the endocrine glands. Deficiency of vitamins A and E causes testicular

17. Stefko, W., cited by Jackson, C. M.: Recent Work on the Effects of Inanition and Malnutrition on Growth and Structure, Arch. Path. **7**:1042 (June) 1929.

18. Waters, H. S.: Capacity of Animals to Grow Under Adverse Conditions, Agric. Sc. **29**:71, 1908; cited by Sherman.[15]

19. Welch, C. S.; Wakefield, E., and Adams, M.: Metabolic Studies in Ulcerative Colitis, J. Clin. Investigation **16**:167, 1937.

20. Smith, A. H.: Phenomena of Retarded Growth, J. Nutrition **4**:427, 1931.

21. Barnes, J. M.: Typical Pellagra Syndrome Developing in Patient with Ulcerative Colitis, Ann. Clin. Med. **4**:552, 1926. Mackie.[8]

22. Thaysen, T. E. H.: Zwei Fälle von idiopathischer Steatorrhoe, mit besonderer Berücksichtigung der Diagnose und des Vorkommens von Symptomen einer Endokrinopathie und Avitaminose, Arch. f. Verdauungskr. **61**:225, 1937; footnote 16.

23. (*a*) McCollum, E. V., and Simmonds, N.: Newer Knowledge of Nutrition, New York, The Macmillan Company, 1929. (*b*) Hogan, A. G.: Riboflavin: Physiology and Pathology, J. A. M. A. **110**:1188 (April 9) 1938. (*c*) Martin, G. J.: Vitamin E, J. Nutrition **13**:679, 1937.

atrophy and inhibition of spermatogenesis.[24] Microscopically the pituitaries of animals so affected show basophilic hyperplasia and have increased gonadotropic effect.[25] This response is similar to, but not as extensive as, that to castration.[26] It is noteworthy that the pituitary in case 2 had a similar microscopic picture. In deficiency of vitamin B_1, diminution in secretion of androgen has been demonstrated.[26a]

The constant loss of calcium often resulting in negative calcium balance in these diseases[27] is important not only in the generalized osteoporosis seen so frequently[28] but in the production of gonadal degeneration and arrest of growth. Simmonds[29] found that the rate of growth of young rats was halved by lowering the calcium intake. Yamasaki[30] found that salt deficiencies as well as vitamin deficiencies resulted in disturbance of spermatogenesis in the testis and follicular atrophy in the ovary. Hirabayshi[31] reported that of all the mineral deficiencies, lack of calcium, magnesium and phosphorus had the most striking effects.

The effects of vitamin deficiencies may tend to enhance and continue the pathologic processes causing them. The production of ulcerative colitis in monkeys by deficiency of vitamin A has been described,[32] and it may be that chronic deficiency of vitamin A in long-standing

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24. (*a*) Sutton, T. S., and Brief, B. J.: Cellular Changes in the Hypophyses of Vitamin A Deficient Rats, Endocrinology **23**:211, 1938. (*b*) Wolbach, S. B., and Howe, P. R.: Tissue Changes Following Deprivation of Fat Soluble A, J. Exper. Med. **42**:753, 1925. (*c*) Mattill, H. A.: Vitamin E, J. A. M. A. **110**: 1831 (May 28) 1938. (*d*) Nelson, W. O.: Studies on the Anterior Hypophysis: Anterior Hypophysis in Vitamine E-Deficient Rats, Anat. Rec. **56**:241, 1933.

25. Mason, K. E., and Wolf, J. M.: Physiological Activity of the Hypophysis of the Rat Under Various Experimental Conditions, Anat. Rec. **45**:232, 1930. Footnote 26.

26. Sutton and Brief.[24a] Nelson.[24d]

26a. Moore, C. R., and Samuels, L. T.: Action of the Testes Hormone in Correcting Changes Induced in Rat Prostate and Seminal Vesicles by Vitamin B Deficiency or Part Inanition, Am. J. Physiol. **96**:231, 1931.

27. Thaysen.[16] Welch, Wakefield and Adams.[19]

28. Bennett, Hunter and Vaughn.[5n] Thaysen, footnotes 5 *b* and 16. Case 2 of this report.

29. Simmonds, N.: Observations on the Rearing of the Young, Am. J. Hyg. **4**:1, 1924.

30. Yamasaki, Y.: Experimentelle Untersuchungen über den Einfluss des Vitamins oder Zellsalzmangels auf die Entwicklung von Spermatozoen und Eiern, Virchows Arch. f. path. Anat. **245**:513, 1923.

31. Hirabayshi, N.: Experimentelle Untersuchungen über den Einfluss der Salze auf die Entwicklung der Spermatozoen bei weissen Mäusen, Virchows Arch. f. path. Anat. **250**:661, 1924.

32. Bellows, J.: Biochemistry of the Lens: Influence of Vitamin C and Sulfhydryls on the Production of the Galactose Cataract, Arch. Ophth. **16**:762 (Nov.) 1936.

gastrointestinal disease may extend the primary pathologic lesions.[33] The adrenal degenerative changes consequent to malnutrition and vitamin deficiency may interfere with the absorption of fat in the utilization of riboflavin.[33a]

The exact role played by these deficiencies in the slowing or halting of cellular metabolism is unknown for the most part, but something is known of the place of the vitamins in the cellular scheme of things. Vitamin B_1 is intimately concerned with the normal metabolism of carbohydrates, more particularly with one of the intermediate products, pyruvic acid. It acts as carrier of oxygen and seemingly is necessary for the completion of normal carbohydrate oxidation.[34] Riboflavin is an essential part of the yellow oxidation enzyme of Warburg and cannot be dispensed with in normal cellular oxidative processes.[35] Vitamin C plays an important role in the redox systems of the cell, probably as a hydrogen acceptor. It has been found that the tissues characterized by high metabolic activity have a high vitamin C content. Such tissues as the interstitial cells of the testes, the anterior and intermediate lobes of the pituitary and the adrenal cortex are the richest sources of vitamin C in the body.[36] Ascorbic acid ranks with glutathione as the most active reducing substance known in living tissues.[37] Bellows found that sulfhydryls and vitamin C were interchangeable in the oxidative-reductive processes of the lens.

In view of the importance of these substances for normal cellular metabolism, it is not surprising that chronic deprivation of them should have considerable effect not only on the organism as a whole but more specifically on the pace makers, the endocrine glands. These organs are so interdependent that a disturbance in one readily affects the others. The effects of such a disturbance can be far reaching. As King [38] said of vitamin C,

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33. Tilden, E. B., and Miller, E. G., Jr.: Response of the Monkey to the Withdrawal of Vitamin A from the Diet, J. Nutrition **3**:121, 1930.

33a. Verzar, F.: Adrenal Cortex and Intestinal Absorption, Am. J. Digest. Dis. & Nutrition **4**:545, 1937.

34. Cowgill, G. R.: Physiology of Vitamin B_1, J. A. M. A. **110**:805 (March 12) 1938. Peters, R. A.: Biochemical Lesion in Vitamin B_1 Deficiency: Application of Modern Biochemical Analysis in Its Diagnosis, Lancet **1**:1161, 1936.

35. Mathews, A. P.: Vitamins, Minerals and Hormones, Baltimore, William Wood & Company, 1937. Hogan.[23b]

36. Biskind, G. R., and Glick, D.: Studies in Histochemistry: Vitamin C in Testes in Relation to Anatomic and to Functional Changes, Arch. Path. **23**: 363 (March) 1937.

37. Hopkins, F. G., and Morgan, E. J.: Some Relations Between Ascorbic Acid and Glutathione, Biochem. J. **30**:1446, 1936.

38. King, C. G.: Vitamin C, Ascorbic Acid, Physiol. Rev. **16**:238, 1936.

a disturbance in the respiratory enzyme systems in the pituitary gland or the corpus luteum, resulting from slight vitamin deficiency may result in physiological disturbances in the . . . [body] which would be difficult to correlate directly with the primary nutritional disturbance.

This statement is just as applicable to the other deficiencies discussed.

In view of the far-reaching effects on growth and maturation of even slight deficiencies, the pathologic changes in cases 1 and 2 are more readily understood. The prepubertal appearance of the testes and the lack of maturation, with total absence of spermatogenesis, in 17 year old boys are similar to findings in malnutrition and deficiency states. The basophilic hyperplasia of the pituitary in case 2 is similar to that in rats deficient in vitamins A and E and implies a compensatory reaction to partial castration.

Despite the importance of nutritional deficiencies in the production of secondary infantilism, they are not the only etiologic agents. Secondary endocrine disturbances may be found when no vitamin deficiency is demonstrable and cannot always be correlated with disturbances in growth.[5a] Such manifestations of endocrine dysfunction are present in chronic diseases when there is considerable variance in the nature of the metabolic upset. Such ailments as chronic heart disease, biliary cirrhosis, hemolytic jaundice, diabetes mellitus and chronic disorders of the gastrointestinal tract disturb the metabolism of the organism in different fashions. Nevertheless, they may all be accompanied or followed by secondary infantilism. It seems, therefore, that any long-continued disturbance of normal metabolic processes taking place during maturation and development may result in secondary infantilism.

SUMMARY

Three cases of infantilism associated with chronic ulcerative colitis are presented. There seems to be no mention of this association in the literature. Further reports of cases are desirable to establish the incidence.

The processes of nutritional deficiencies in the chronic diarrheas are pointed out, and their role in the production of secondary infantilism is discussed.

The role of other metabolic disturbances in chronic diseases is mentioned.

RECURRING ENCEPHALOMENINGORADICULITIS WITH FIBROMYOSITIS FOLLOWING POLIOMYELITIS

A BACTERIOLOGIC STUDY OF SIXTY-FOUR CASES

EDWARD C. ROSENOW, M.D.
ROCHESTER, MINN.

It is the purpose of this paper to describe the methods used and to record the results obtained in a study made in July 1937 of 64 cases (in most of which the patients were nurses) of a strange recurring infection, well designated, according to the tissues chiefly affected, as encephalomeningoradiculitis and fibromyositis.

In most instances the illness began during an epidemic of poliomyelitis in 1934; in others it began during lesser outbreaks in 1935 and 1936. Acute anterior poliomyelitis was the original diagnosis in most of the cases. The original attack, although usually atypical,[1] was probably referable to the virus of poliomyelitis as well as to the streptococcus.[2] The virus was demonstrated in the nasopharynges of ill persons by Paul, Trask and Webster[3] and in the spinal cord at autopsy by Kessel, Hoyt and Fisk[4] as well as Rosenow, Heilman and Pettet.[5] Streptococci were isolated consistently from the nasopharynx, spinal fluid and spinal cord by Rosenow, Heilman and Pettet. Recovery from the primary attack in many instances was sufficient to permit the patients to return to work for from three weeks

From the Division of Experimental Bacteriology, the Mayo Foundation.

1. Hart, T. M., and Luck, J. V.: Orthopedic Aspect of the Los Angeles County 1934 Poliomyelitis Epidemic, Am. J. Pub. Health **24**:1224-1228 (Oct.) 1934.

2. Rosenow, E. C.: The Relation of Streptococci to the Viruses of Poliomyelitis and Encephalitis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **10**:410-414 (June 26) 1935.

3. Paul, J. R.; Trask, J. D., and Webster, L. T.: Isolation of Poliomyelitis Virus from the Nasopharynx, J. Exper. Med. **62**:245-257 (Aug.) 1935.

4. Kessel, F. J.; Hoyt, A. S., and Fisk, R. T.: Use of Serum and the Routine and Experimental Laboratory Findings in the 1934 Poliomyelitis Epidemic, Am. J. Pub. Health **24**:1215-1223 (Oct.) 1934.

5. Rosenow, E. C.; Heilman, F. R., and Pettet, C. H.: Observations on the Epidemic of Polio-Encephalitis in Los Angeles, 1934, Proc. Staff Meet., Mayo Clin. **9**:443-451 (July 25) 1934.

to three months, at the end of which time increasing weakness, fatigability, pain in muscles and attacks of recurring headaches forced them to bed despite every known treatment.

CLINICAL OBSERVATIONS

Most of the patients having severe forms of the disease at the time of this study were hospitalized. They had received every possible care. On inquiry, it was learned that the exacerbations in many of the patients studied who were residing in the same hospital had occurred almost simultaneously. The attacks were characterized by severe headaches, which often were continuous for weeks and were associated in varying degree and frequency with low grade fever, projectile vomiting, occasional diarrhea, transient diplopia, blurred vision, dizziness, incoordination, photophobia, pain behind the eyeballs, deep-seated pain in the back and extremities, extreme nervous irritability, sleeplessness, emotional instability, severe mental depression and muscular weakness and tenderness.

Extreme dysmenorrhea was a common complaint. Sclerotic, cystic ovaries were found and in some cases were removed by operation. Retention of urine caused by paresis of the bladder or stricture of the ureters, with resulting infections, occurred in some cases and was commonly relieved by the use of retention catheters and by ureteral catheterization. Other complications included long-continued superficial hyperesthesias of the skin, deep muscular and musculotendinous tenderness, pain and tenderness of the rheumatic type in the heels and wrists and painful joints. A history of recurring attacks of urticaria was elicited from 17 of 53 patients. A striking finding in several instances was fibrous ankylosis of the interphalangeal joints of the hands of such severity that the fingers could not be clenched into a fist.

Certain patients had reacted favorably to care by well trained physical therapeutists, who had applied local heat and massage and had tried individually supervised exercises. Many patients who had experienced mild attacks had returned to part time or full time duty. A considerable number reported that they had fared well with rest, without physical therapy. Hyperactivity rather than diminution or absence of tendon reflexes was the rule, even in the presence of widespread muscular weakness without proportionate atrophy. Muscles of good size were apparently present and could be caused to contract voluntarily but without much power. Tonic and clonic spasms of muscles were common, some muscles even requiring application of a cast for their control. Paroxysmal tachycardia, with rapid, thready pulse, attacks of pseudoangina and recurring attacks of mild sore throat and diarrhea were not uncommon. Most striking of all observations concerning

muscular involvement were the universal lack of muscular endurance, the variability of response and strength and the early tiring and exacerbations which were often directly attributable to mental and physical overexertion. The muscles of the abdomen and of the region of the hip were most often affected. Localized paralysis and wasting of muscle groups, such as are seen in typical infantile paralysis, were uncommon.

In short, there was apparent almost every conceivable combination of symptoms and findings referable to purely functional or mental disturbances, as generally understood, and also to physical diseases; yet almost none of these was typical of any well known disease. Clinically the condition in some of the cases resembled the infectious neuronitis described by Kennedy [6] and the "myeloradiculitis" described by Strauss and Rabiner.[7] Wilson and Walker [8] reported that the early observations during and soon after the epidemic of 1934 were different from those which characterize typical epidemic poliomyelitis. Unique were the high incidence (about 10 per cent) of poliomyelitis among nurses and physicians while they were caring for the sick and the large number of persons who had recurring exacerbations. The usual sex incidence of poliomyelitis was reversed among patients who had recurring attacks, the number of females afflicted being three times that of males. Older children and young adults were stricken chiefly. This was true also during the large outbreak in Denmark in 1934. The late manifestations of the disease, however, did not appear during the latter epidemic.[9]

Rosenow, Heilman and Pettet [5] also stressed the atypical character of the primary disease and reported results observed in animals inoculated with streptococci isolated consistently from the nasopharynges, spinal fluid, brains and spinal cords of patients. These results differed from those usually obtained in similar studies of typical epidemic poliomyelitis. The incidence in the inoculated animals of flaccid paralysis like that observed in patients at the time of the epidemic was not so high, but evidences of pain were more numerous and the incidence of muscular spasms and lesions of the muscles was higher.

6. Kennedy, F.: Infective Neuronitis, Arch. Neurol. & Psychiat. **2**:621-627 (Dec.) 1919.

7. Strauss, I., and Rabiner, A. M.: Myeloradiculitis: A Clinical Syndrome, with a Report of Seven Cases, Arch. Neurol. & Psychiat. **23**:240-256 (Feb.) 1930.

8. Wilson, J. C., and Walker, P. J.: Acute Anterior Poliomyelitis: Orthopedic Aspects of the California Epidemic of 1934, Arch. Int. Med. **57**:477-482 (March) 1936.

9. Jensen, C.: The 1934 Epidemic of Poliomyelitis in Denmark: Preliminary Report on the Epidemiology and Clinical Features and Convalescent Serum Therapy, Proc. Roy. Soc. Med. **28**:1007-1026 (June) 1935.

METHODS AND SCOPE OF STUDY

On the basis of these observations it was thought that a bacteriologic study by methods which I have previously described and by means of serologic tests recently developed might throw light on the causation of this complex syndrome. Cultures in dextrose–brain broth and other mediums were made from material obtained by swabbing the nasopharynx and the uterine cervix, from the urine and feces, from the blood and cerebrospinal fluid and from excised specimens of affected muscles and ovaries. Animals—mice, rabbits and monkeys—were given injections of the organisms thus freshly isolated. The cataphoretic velocity of the streptococci was determined by methods previously described, without knowledge of the condition of the patient or of whether the culture tested was obtained from controls.[10] Cutaneous, precipitation and agglutination tests were made with

10. I am aware of the skepticism of some regarding the value of cataphoretic studies on streptococci. By virtue of strict attention to technical details my associates and I have obtained consistent results in such a variety of diseases as to convince us of the value of such studies. Others have reported similar results.[6] The differences in the results obtained by different workers are largely attributable to differences in technic—to the small number of strains tested, to the time of the study, to the type of mediums used and to faults of interpretation. It has been shown that seasonal changes occur in the cataphoretic velocity of streptococci (Rosenow, E. C., and Jensen, L. B.: Cataphoretic Velocity of Streptococci Isolated in Cases of Encephalitis and of Other Diseases of the Nervous System, J. Infect. Dis. **52**:167-184, 1933). The determination of the cataphoretic time and velocity of streptococci has significance almost never, except when the strain used has been freshly isolated (Rosenow, E. C., and Davis, C. H.: The Bacteriology and Experimental Production of Ovaritis, J. A. M. A. **66**:1175-1180 [April 15] 1916). We have found that mediums to which brain tissue has been added before autoclaving, such as dextrose–brain broth, are especially favorable to the isolation of pathogenic streptococci. This point has been corroborated by Burdon and his associates (Burdon, K. L.; Thurston, E. W.; Varney, P. L., and Bronfenbrenner, J.: The Etiologic Significance of Streptococci in Epidemic Encephalitis: I. Incidence of Streptococci in Cultures from Patients with Encephalitis in St. Louis and from Normal Controls, and Characteristics of the Various Strains Isolated, Arch. Int. Med. **58**:285-308 [Aug.] 1936; II. Experiments with Animals and Conclusions, ibid. **58**:469-494 [Sept.] 1936). Such mediums are also favorable to the maintenance of elective localizing power and (concomitantly) characteristic cataphoretic velocity (Rosenow, E. C., and Ashby, W.: Focal Infection and Elective Localization in the Etiology of Myositis, ibid. **28**:274-311 [Sept.] 1921). In our extensive experience with primary dextrose–brain broth cultures of material from the nasopharynges of persons suffering from encephalitis or other epidemic diseases, my associates and I have never found that long chains of streptococci or contaminating organisms were present in sufficient number to alter perceptibly the distribution curves of cataphoretic time velocity, which these investigators suggest as possible sources of error. Moreover, I have shown that the distribution curves of cataphoretic time and velocity of the streptococci which grew in the primary culture in dextrose–brain broth were not only characteristic of, but were nearly identical with, the distribution curves of the streptococci that had grown not in the culture mediums but in the nasopharynx or in foci of infection elsewhere and that were timed directly. The discrepancies, or what

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serums obtained from patients and with different antistreptococcic serums from immunized horses.

Nearly all material was inoculated on blood agar plates for detection of aerobes and into deep tubes of dextrose–brain broth for the isolation of partial oxygen tension or anaerobic organisms. The amount of inoculum varied greatly for different tubes of medium. In some instances the spinal fluid was incubated after layering with sterilized linseed oil. Cultures were also made by dipping swabs coated with coagulated horse serum into the spinal fluid and incubating these and by layering the spinal fluid over Löffler's blood serum slants. Blood was drawn from the patient in a sterile manner and placed in vacuum vials, where it was allowed to clot. The serum was removed, and the partially macerated clot was transferred with sterile precautionary measures to dextrose–brain broth.

Dextrose–brain broth, the medium chiefly used, was freshly prepared by adding pieces of brain from calves slaughtered on the same day to an infusion or extract broth to which 0.2 per cent dextrose and Andrade's indicator were added. The reaction was brought to a p_H of 7, and the medium was placed in columns of from 10 to 12 cm. in height in deep tubes (20 by 1.5 cm.). Pieces of brain representing a volume of from 2 to 3 cc. for each tube were added before autoclaving

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Burdon, Thurston, Varney and Bronfenbrenner interpreted as such, in the distribution curves of cataphoretic velocity of the streptococci isolated in their and our studies of the St. Louis epidemic of encephalitis are explicable on the basis of their use of strains too long after isolation and also on the basis of the difference in time of study. Our study was made during hot weather (summer), at the height of the epidemic; theirs was conducted during cooler weather (autumn), after the epidemic had largely subsided. Their average distribution curve of cataphoretic velocity of the streptococci freshly isolated in cases of encephalitis stacked at nearly the "neurotropic" cataphoretic time of 2 to 2.5 seconds, while that of the strains freshly isolated from the nasopharynges of well controls stacked markedly at nearly the "pharyngotropic" time of 3.5 seconds. The three groups of strains that had been cultivated for some time on artificial mediums likewise stacked heavily at nearly 3.5 seconds. Their results approximated precisely what one would expect. The curve of the streptococci freshly isolated in the cases of encephalitis approached the "neurotropic" type at nearly the cataphoretic time of 2 seconds, instead of mainly at 4 seconds. The former type in our studies was obtained especially at the onset of acute attacks; the latter, at a later time, during attacks. Both types have been shown to have neurotropic virulence. All of the other four groups of strains approximated the "pharyngotropic" type at nearly 3.5 seconds, which is obtained in streptococci freshly isolated from the nasopharynges of persons suffering from the common or autumnal cold and to a lesser degree in streptococci from the nasopharynges of well persons in autumn during epidemics of colds (Rosenow and Jensen). Shifts in cataphoretic velocity of streptococci according to seasons such as these, unsuspectingly determined by Burdon and his associates, have been repeatedly noted of streptococci freshly isolated from the nasopharynges of well persons (Rosenow and Jensen) and simultaneously, or nearly so, of streptococci in cases of encephalitis and other diseases as kept in dextrose–brain broth cultures in the laboratory. By the strictest attention to technical details and by having the operator make readings of cultures without knowledge of the condition of the patient or of whether the organisms were obtained from controls, we have again obtained by our method, as will be shown, information of importance as regards the nature of the strains from different patients in the group under study.

at 20 pounds (9.1 Kg.) of pressure for twenty minutes. In some instances the dextrose–brain broth was placed in hermetically sealed bottles of from 15 to 120 cc. capacity. The inoculated mediums were incubated at 35 C. (95 F.).

Mice were given injections of cultures or direct injections of spinal fluid or other material, 0.03 cc. intracerebrally and (usually) 2.5 cc. intraperitoneally. Rabbits and monkeys were inoculated intracerebrally and/or intravenously with cultures or directly with material obtained from patients and other sources. The dose varied between wide limits, depending on the nature of the material under study. Routinely, 0.1 cc. of a suspension of swabbings from the nasopharynx or from the uterine cervix in 2 cc. of saline solution was injected intracerebrally, and 0.1 cc. of a 1:200 or 1:1,000 dilution of the dextrose–brain broth culture and 0.5 cc. of the undiluted culture for each 100 Gm. of body weight were injected intravenously into rabbits and monkeys. In special instances the doses were much less, sometimes a thousandfold less, yet positive results were obtained. The animals were observed repeatedly every day for symptoms and were examined for lesions as soon after death as was possible. Those that survived were etherized to death within from three to fourteen days after inoculation. The excised muscles, ovaries and tissues of animals were fixed in solution of formaldehyde U. S. P. diluted 1:10, and paraffin sections were stained with hematoxylin and eosin and by the Gram method. In the latter procedure, however, no counterstain was used, and decolorization was carried out only to a fair blue instead of to the end point.

Precipitation tests[11] were made with saline extracts of nasopharyngeal swabbings and with the serums of patients. These were layered in small tubes over the serums of horses hyperimmunized with streptococci isolated during studies of encephalitis, poliomyelitis, arthritis and ulcerative colitis. As controls, the extracts and serums from patients were also layered over the antiserums after absorption of the latter with the homologous streptococci. Clouding at the interphase with the unabsorbed antiserum and the absence of clouding or clouding of lesser degree with the absorbed serum indicated the presence in the throat or serum of the patient of a streptococcic antigen immunologically related to the streptococci with which the reacting antiserum had been prepared.

Cutaneous tests were made by injecting intradermally 0.05 cc. of a 10 per cent solution in saline of the euglobulin (antibody) fraction of the antiserum. The antiserums used were those of horses hyperimmunized to different streptococci and those (diluted 1:10) of persons convalescing from acute exacerbations of the disease. An erythematous–edematous reaction within ten minutes after injection of the antiserum or convalescent serum indicated the presence in the skin or blood of an antigen immunologically related to the streptococci with which the reacting serum had been prepared[11] and to the infective streptococci in the patient from whom the convalescent serum (antibody) had been obtained. In every case the estimation of the degree of reaction was concurred in by two or more observers.

Agglutination tests were made with strains of the streptococci isolated from the nasopharynx, stools, uterine cervix, urine, blood, spinal fluid and muscles. Agglutination experiments were done according to a special technic which we have found essential to the securing of evidence of the presence of streptococcic

11. Heilman, F. R., and Rosenow, E. C.: Newer Methods of Study and Treatment of Chronic Streptococcal Disease, Proc. Staff Meet., Mayo Clin. **12**:252-256 (April 21) 1937.

agglutinins in the serums of patients with chronic streptococcic diseases and patients with acute poliomyelitis and encephalitis. The streptococci freshly isolated in dextrose–brain broth were centrifuged, the supernatant broth was poured off, the organisms were suspended in small amounts of glycerin (2 parts) and 25 per cent salt solution (1 part), and from this dense suspension dilutions were made to the density of a dextrose–brain broth culture. These diluted suspensions were then mixed in 0.2 cc. amounts with 0.2 cc. amounts of the respective dilutions of serum in Wassermann tubes. The mixtures were incubated at 50 C. (122 F.) for eighteen hours and then read.[12]

12. Pertinent to the problem under consideration, I wish here to point out wherein lay the inability of some investigators to corroborate the results obtained in our studies on streptococci in encephalitis. By the use of this method of agglutination we found, contrary to the results obtained by Burdon, Thurston, Varney and Bronfenbrenner, that the serum of patients convalescing from encephalitis in St. Louis agglutinated more strongly and in much higher dilution the streptococci isolated consistently from the nasopharynx, spinal fluid and brain in our study made during the height of that epidemic than did the serum of well controls. Considering the confirmatory results obtained in other respects, it is unfortunate that the aforementioned investigators tested the agglutinating power of convalescent serum on strains of streptococci after those strains had been cultivated on artificial mediums for some time instead of on freshly isolated strains, making suspensions directly from cultures instead of from dense glycerin–saline solution suspensions, incubating the mixtures at 37 C. (98.6 F.) for only one and a half hours and then placing them in the ice chest overnight instead of incubating them at 50 C. (122 F.) for eighteen hours. We, also, did not get agglutination when we proceeded under such conditions. Also pertinent to this study is the fact that these investigators seem to have missed the point that animals which after injection of streptococci survived the acute symptoms and later showed manifestations of encephalitis and which succumbed or were anesthetized late almost always exhibited typical perivascular lymphocytic infiltrations in the brain. Burdon, Thurston, Varney and Bronfenbrenner showed photomicrographs only of acute lesions, and, of course, the infiltrating cells to be seen in these were mainly polymorphonuclear leukocytes, a finding which is in accord with the fact that in the very early stages of the disease in the human being these cells are often present in the spinal fluid, sometimes in predominating numbers.

Whether the streptococcus played the role of an important secondary invader in that epidemic, as was concluded by them, or whether the streptococcus played the primary role and the virus the secondary one, it is impossible to decide on the basis of published data now available. A forthcoming report will contain important information on the relation of the streptococcus to the virus of encephalitis.

McKinley's report (McKinley, E. B.: Failure to Confirm Rosenow's Work on Encephalitis in Its Relation to Green Streptococcus, Proc. Soc. Exper. Biol. & Med. **27**:436-440 [Feb.] 1930) I have disregarded because he injected, as far as I can tell, into only 2 rabbits streptococci from the nasopharynges of 25 well persons in Puerto Rico and only 1 patient with encephalitis. However, since Burdon, Thurston, Varney and Bronfenbrenner attach significance to his work, I am impelled to state that if he had injected highly diluted cultures (as high as 1:1,000,000), as we did, instead of only our maximal dose (0.2 cc.)

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RESULTS OF CULTURES AND OF SEROLOGIC STUDIES

Blood agar platings directly from swabbings of the nasopharynx and the uterine cervix, or from the primary growth in dextrose–brain broth, yielded uniformly a large number of green-producing streptococci or indifferent colonies of streptococci and almost never hemolytic streptococci. The primary cultures in dextrose–brain broth uniformly yielded pure or almost pure cultures of streptococci (fig. 1 *A*). Green-producing streptococci were repeatedly isolated in large numbers from specimens of stools obtained during exacerbations of symptoms. The results of cultivation of specimens of the blood, spinal fluid, muscles, ovary and catheterized urine are summarized in table 1.

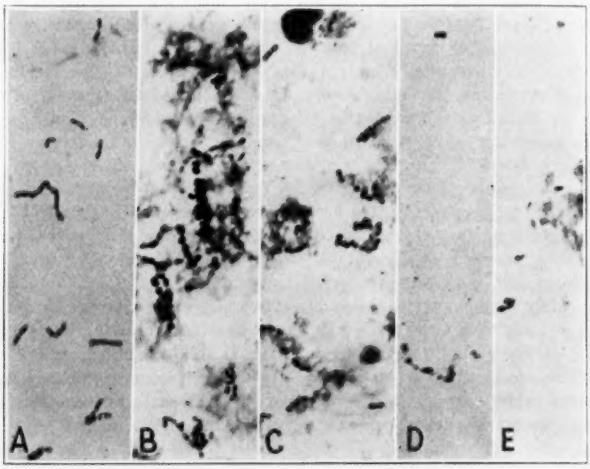

Fig. 1.—Streptococci as isolated in dextrose–brain broth, from (*A*) nasopharyngeal mucus, (*B*) blood, (*C*) spinal fluid, (*D*) cystic fluid from ovary and (*E*) excised muscle. Rosenow-Gram stain; × 1,000.

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of the suspension of material from the nasopharynx and tonsils, he would no doubt have obtained not only the early acute manifestations of meningoencephalitis but the late more typical symptoms and lesions, as have we. Differentiation by the agglutination reaction of green-producing streptococci from throats of well persons and persons with encephalitis or poliomyelitis was possible only in dilutions of the antiserums which I sent him above those which he used. The demonstration in the throats of well persons of green-producing streptococci which have early effects in rabbits like those of the streptococci in encephalitis does not disprove the etiologic importance of the streptococcus in encephalitis any more than the demonstration of the diphtheria bacillus in the throats of well persons disproves the etiologic importance of the diphtheria bacillus in diphtheria.

Cultures of blood clot were made in freshly prepared dextrose–brain broth in 64 cases. In Glendale the cultures were made within four hours and in Rochester within forty-eight hours after drawing the blood. The organisms obtained are represented in figure 1. All the cultures made in Rochester remained sterile, while those made at once in Glendale yielded streptococci (fig. 1 *B*) roughly in proportion to the severity of the symptoms in the patients. Only rarely were streptococci isolated from healthy exposed persons, and at Rochester they were never grown from blood of nonexposed persons. Thus, as is shown in table 1, streptococci were isolated from only 3 (13 per cent) of 24 patients with mild symptoms, from 12 (63 per cent) of 19 patients with severe symptoms at the time the blood was drawn and from only 1 (5 per cent) of 21

TABLE 1.—*Results of Culture of Materials Obtained in Patients with Recurring Encephalomeningoradiculitis and Fibromyositis and from Others*

Material Cultured	Source	Total Number	Number with Cultures Positive for Streptococci	Percentage* with Cultures Positive for Streptococci
Blood	Patients with given type of involvement			
	Severe	19	12	63
	Mild	24	3	13
	Recovered	21	1	5
	Exposed persons	15	5	33
	Control nurses			
	Glendale, Calif.	18	0	0
	Rochester, Minn.	45	0	0
Spinal fluid	Patients with severe involvement	14	13	93
Excised muscles		5	4	80
Ovary		1	1	100
Catheterized urine		15	8	53

* Percentages are given to the nearest whole number.

persons who had returned to work. Streptococci were isolated from the blood of 5 (33 per cent) of 15 nurses and physical therapeutists who were in close contact with the disease, some of whom complained of undue fatigability and other symptoms. In no instance were streptococci isolated from the blood of three groups of nonexposed nurses, one group consisting of 18 residing in the epidemic zone, the others consisting of 27 and 18, respectively, residing outside of the epidemic zone. Through the assistance of Dr. F. E. Poole, of Glendale, 1 or 2 specimens of spinal fluid obtained from each of 14 patients having active infections were made available. The cell count was extremely low in all specimens; 9 disclosed the presence of one cell per cubic millimeter, 8 showed two cells, 2 showed three cells and 2 showed four cells. Extremely pleomorphic gram-positive to gram-negative diplostreptococci were isolated from the spinal fluid of 13 of the 14 patients (fig. 1 *C*). The bacteria

obtained from the spinal fluid did not always grow out as typical streptococci when they were cultivated in artificial mediums, but those from the brains of mice and rabbits that died in from three to eight days after intracerebral inoculation of the atypical cultures and those in specimens of spinal fluid plated directly usually did. Cultures were made of catheterized urine from 15 patients, and 8 of the cultures showed growth of streptococci.

Excised pieces of tender muscle from 5 patients were cultured and examined microscopically. Three of these yielded pure cultures of extremely pleomorphic streptococci (fig. 1 *E*). One yielded streptococci with diphtheroid bacilli and micrococci (sometimes all three forms were present in the same chain). One remained sterile, and sections showed no lesions. The 4 specimens yielding streptococci showed irregular staining and degeneration of muscle fibers, fibrosis, and perivascular and other infiltration by mononuclear cells and scattered diplococci in or adjacent to the lesions (figs. 2 and 3). One cystic ovary (from a patient who suffered almost intolerably at the menstrual period) became available for study. Extremely pleomorphic streptococci (fig. 1 *D*), especially resembling those from the spinal fluid and muscles (fig. 1 *C* and *E*), were isolated in dextrose–brain broth from the cystic fluid of this ovary, from pieces and also from emulsions of the tissue. Sections disclosed the presence of advanced fibrosis, cellular infiltration in the walls of the cysts, a few diplococci in the walls of the cysts and large numbers of diplococci in the coagulated albuminous film in the lumens of the cysts (fig. 4).

The incidence of positive reactions to precipitation tests, indicating the presence of an antigen related to the streptococci with which the reacting antiserum was prepared (table 2), was highest with the nasopharyngeal extracts and the serums from patients having active infections, next highest with those from exposed persons and lowest with those from nonexposed persons, when these extracts and serums were layered over antiserums prepared with streptococci isolated respectively from persons with chronic encephalitis (neurotropic strains) and from persons with chronic infectious arthritis (arthrotropic strains).

The immediate erythematous reactions [11] to the different antiserums (indicating the presence of antigen in the skin related to the streptococci with which the reacting antiserums were prepared) varied greatly in different patients. The greatest reaction was usually that to an antiserum prepared with streptococci isolated from a disease in which the symptoms were most nearly like those of the patient at the time of the test. Thus if neuritic pains, so common during the epidemic (radiculitis), were marked, the greatest erythematous reaction was that to the antiserum prepared from strains isolated during studies of the Los

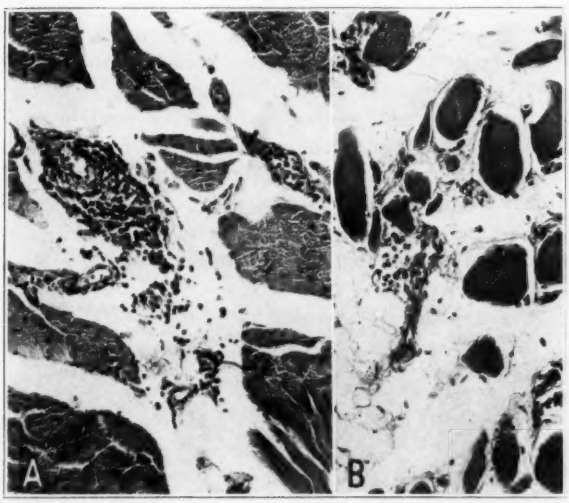

Fig. 2.—Edema and perivascular and interstitial cellular infiltration of excised muscles of 2 patients who had severe pain referable to muscles. Hematoxylin and eosin stain; × 150.

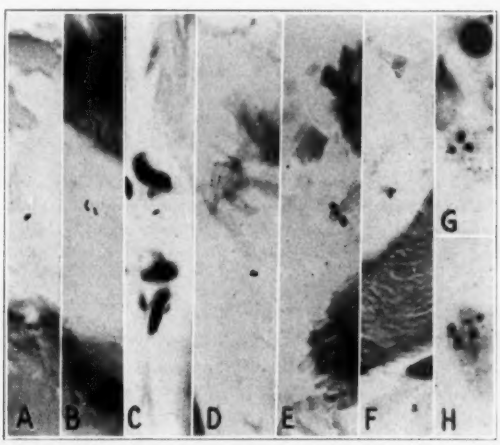

Fig. 3.—Pleomorphic diplococci in the lesions of muscles shown in figure 2. Rosenow-Gram stain; × 1,000.

Angeles epidemic of poliomyelitis. If, however, muscular or rheumatic symptoms of myositis with or without arthritis predominated (which was the rule), the greatest erythematous reaction was observed when the antiserum prepared with streptococci isolated in studies of arthritis was used. If involvement of muscles associated with undue fatigability was especially marked, the greatest erythematous reaction was that to the antiserum prepared with streptococci from patients with myasthenia gravis. The average reactions of all the groups tested with the different antiserums are given in table 3.

The reason for the relatively high incidence of precipitation reactions with the polioencephalitis and arthritis antiserums (table 2) and the

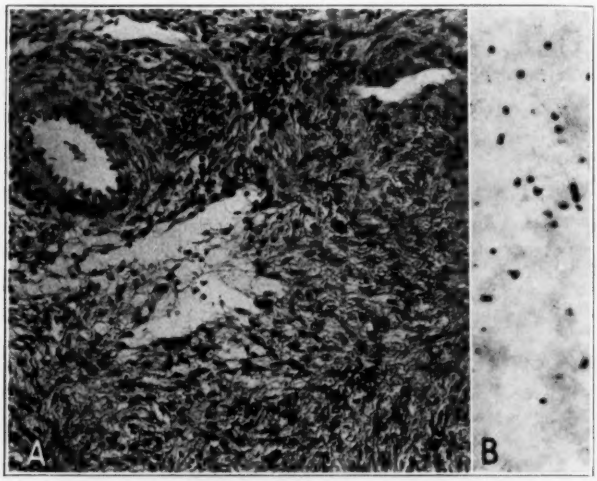

Fig. 4.—*A*, edema, degeneration, fibrosis and cellular infiltration and (*B*) diplococci in the ovary removed surgically from a patient who had almost intolerable pain during menstruation. (*A*, hematoxylin and eosin stain, × 150; *B*, Rosenow-Gram stain, × 1,000.)

serums from the group of nurses at hospital A (Rochester) used as antigen and of the relatively marked cutaneous reactions (table 3) is not entirely clear. It is possible that streptococci similar to those isolated during our study of the cases in 1934, which we isolated from the drinking water of the group of nurses at hospital A (Rochester) at the time of the study, might have been responsible. The streptococci isolated produced lesions of muscles, fascia and nerve sheaths after intracerebral and intravenous injection. Several nurses had mild symptoms resembling those arising from neurofibromyositis shortly before or at the time,

TABLE 2.—*Precipitation Reactions Between Antistreptococcic Serums and (1) Cleared Saline Extracts of Nasopharyngeal Swabbings and (2) the Serums of Patients*

Source of Antigen	Groups	Number	Percentage* with Positive Reactions to Serums from Horses Hyperimmunized with Streptococci from Patients Ill with					Control: Percentage with Reactions to Normal Horse Serum (1:10)
			Chronic Encephalitis	Acute Encephalitis (St. Louis)	Polioencephalitis (Los Angeles)	Chronic Infectious Arthritis	Ulcerative Colitis	
Naso-	Patients	55	49	18	11	43	18	2
pharynx	Exposed persons	41	19	10	5	34	10	2
	Nonexposed persons							
	Glendale, Calif.	17	6	0	0	19	0	0
	Rochester, Minn.	47	6	6	4	4	6	0
Serum	Patients	62	55	21	16	29	15	0
	Exposed persons	35	54	6	17	11	14	0
	Nonexposed persons							
	Nurses, Glendale, Calif.	18	44	6	22	17	0	0
	Nurses, Hospital A, Rochester, Minn.	26	27	8	8	15	0	0
	Nurses, Hospital B, Rochester, Minn.	18	6	0	0	6	0	0

* Percentages are given to the nearest whole number.

TABLE 3.—*Results of Intradermal Tests with the Euglobulin (Bacterial Antibody) Fractions of Serums of Horses Hyperimmunized with Different Types of Streptococci*

Group	Number	Average Reaction (Sq. Cm.) to Antibodies in Serums Prepared with Streptococci from Patients Ill with							Control: Average Reaction to Normal Horse Serum (1:10)
		Polioencephalitis (Los Angeles)	Typical Poliomyelitis	Chronic Encephalitis	Acute Encephalitis (St. Louis)	Chronic Infectious Arthritis	Ulcerative Colitis	Myasthenia Gravis	
Patients with active infection	40	7.5	6.6	3.0	6.4	13.0	3.4	6.6	1.6
Convalescent patients									
Severe symptoms*	29	5.6	4.8	2.0	2.4	10.3	3.3	3.8	1.3
Mild symptoms*	46	3.7	3.5	1.3	2.3	6.6	1.8	1.9	1.4
Exposed persons (nurses and physical therapeutists)	37	3.7	3.3	1.2	3.0	7.5	1.9	2.7	1.2
Nonexposed persons									
Nurses and other hospital personnel, Glendale and Los Angeles, Calif.	39	1.7	1.4	1.28	1.5	6.9	1.0	2.1	0.6
Nurses, Hospital A, Rochester, Minn.	27	4.8	...	1.0	...	4.4	...	1.4	1.6
Nurses, Hospital B, Rochester, Minn.	18	2.8	...	0.7	...	2.1	1.7	0.7	0.8

* At the time of the test.

and similar cultures of the drinking water of the group of control nurses at hospital B (Rochester), among whom the incidence of precipitation and cutaneous reactions was much lower, failed to reveal streptococci. Because of the great differences as to the chief complaint in the different cases, the average size of the area of reaction does not adequately express how specific or diagnostic these cutaneous reactions were. The degree of reaction to the "homologous" antiserum was usually directly proportional to the severity of symptoms. Similar results were obtained after intradermal injection of the serum (antibody) obtained from patients during convalescence from acute exacerbations of the disease. Thus, in 10 patients having acute attacks the average area of erythematous reaction to the serum obtained from a patient recovering from an exacerbation was 9.7 sq. cm.; in 17 convalescent patients it was 4.8 sq. cm. and in 27 healthy exposed persons it was 3.4 sq. cm. To the serum of a well

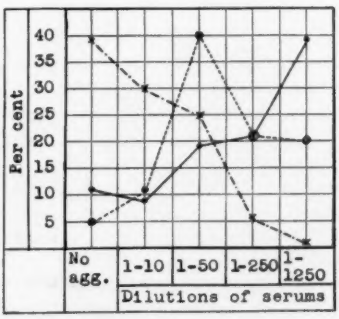

Fig. 5.—Absence and end point of agglutination of the streptococci by the serums of 50 patients in 133 tests (solid line) of 21 exposed persons in 41 tests (dotted line) and of 26 nonexposed persons in 88 tests (dot and dash line).

person of the same age and sex the areas of reaction were 2.3, 1.0 and 1.8 sq. cm., respectively, in the same three groups of subjects.

The agglutinating power of individual serums and of pools of six serums from patients, exposed persons and nonexposed persons over separate strains and pooled strains of streptococci was determined under comparable conditions. The results of the agglutination experiments are summarized graphically in figure 5. The incidence of nonagglutination was much higher when serums from nonexposed persons were used than when serums from patients and exposed persons were used. The end point of agglutination became progressively higher with increasing dilutions of the serum from patients, less so with the serum from exposed persons and progressively lower with the serum from nonexposed persons. In addition, the serums from these patients especially agglutinated

the pooled suspensions of streptococci from patients with arthritis, neuromyositis or myasthenia gravis, suspected material to which the patients were exposed and, to a lesser degree the streptococci isolated during the epidemic. These serums did not agglutinate the streptococci obtained from patients with acute encephalitis.

The average distribution curves of cataphoretic velocity of the streptococci obtained from patients and exposed persons, without regard to the cutaneous reactions and according to whether cutaneous reactions occurred to the "arthrotropic" or the different "neurotropic" serums were determined by methods previously described and are summarized in figure 6. It will be seen that the distribution curve of cataphoretic velocity of streptococci isolated from patients and exposed persons without regard to the cutaneous test covered a wide range, with maximal

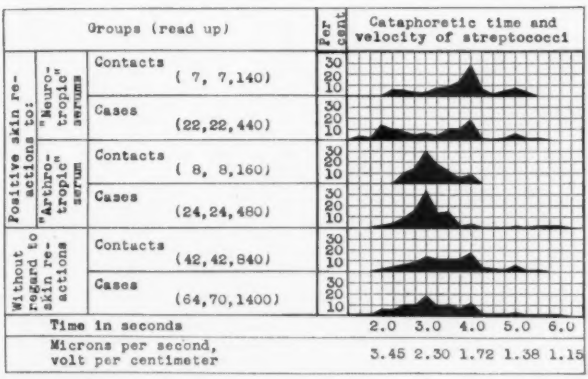

Fig. 6.—Cataphoretic time and velocity of streptococci isolated from the nasopharyngeal mucus of patients having recurring attacks of encephalomeningoradiculitis and fibromyositis and also from the nasopharyngeal mucus of exposed persons. The figures in parentheses indicate, respectively, the numbers of strains, cultures and streptococci timed in each group.

numbers occurring in the "arthrotropic" and "neurotropic" columns (2.30, 3.45 and 1.72 microns per second, volt per centimeter). The streptococci from the nasopharynges of patients and exposed persons who reacted strongly in the cutaneous test to the "arthrotropic" serum and whose symptoms at the time were mainly referable to connective tissue and muscle had an "arthrotropic" distribution curve, and the streptococci from persons who reacted strongly to one or more serums prepared with streptococci from persons who had disease of the nervous system and symptoms referable chiefly to the nervous system had a "neurotropic" distribution curve.

RESULTS IN ANIMALS OF INTRACEREBRAL AND INTRAVENOUS INOCULATION OF THE ISOLATED STREPTOCOCCI

Since the condition in most of the patients under study began during the epidemic of atypical poliomyelitis in 1934, I have summarized for comparison the results obtained in experiments with streptococci isolated at that time and the results of similar experiments performed with streptococci isolated from patients suffering three years later from this strange combination of recurring symptoms of encephalomeningo-

TABLE 4.—*Mortality, Symptoms and Incidence of Lesions Among Animals Inoculated with the Isolated Streptococci*

Source of Streptococci	Time of Study	Method of Inoculation	Species	Strains	Animals: Inoculated	Animals: That Died	Animals Showing Given Symptom: Pain	Paralysis	Spasms	Fatigability	Animals Showing Lesions of: Brain and Cord	Dura	Nerve Roots	Muscles and Fascia
Nasopharynx, spinal fluid, brain and cord of patients	1934	IC* or IV†	Rabbit and monkey	13	93	71	19	32	13	..	84	19	15	16
Nasopharynx, cervix, urine, stool, blood, spinal fluid, muscle and ovary of patients	1937	IC	Rabbit and monkey	28	32	69	50	16	41	41	25	28	28	72
		IV	Rabbit	11	15	60	47	13	20	47	33	..	..	80
		IC and IV	Rabbit	9	17	88	30	18	41	41	24	41	60	88
		IC and IV	Monkey	6	6	66	100	33	33	67	33	83	83	100
		Total.....		39	70	71	49	17	36	44	27	30	49	80
Nasopharynx (well exposed persons)	1937	IC	Rabbit	15	16	50	6	13	6	0	0	6	6	6
Filtrates of nasopharyngeal washings	1937	IC	Rabbit and monkey	10	17	0	0	0	0	0	0	0	0	0

* Intracerebral. † Intravenous.

radiculitis and fibromyositis, from exposed persons and from other sources.

In the present study the results after injection of the streptococci isolated from the swabbing of the nasopharynx and cervix and from blood, urine, stool, spinal fluid, excised muscles and ovaries were strikingly similar to those obtained in the earlier study. The observations following intracerebral and intravenous injection of streptococci into rabbits and monkeys are summarized in table 4. During the epidemic and three years later the mortality of the animals was consistently high and was always higher than after injection of streptococci from healthy exposed persons. The incidence of the chief symptoms and lesions in

the two groups of experiments paralleled in general, and often strikingly, that in the patients from whom the streptococci were obtained. This was true particularly as regards evidence of pain (especially pain referable to the head and muscles), weakness or paralysis, fatigability and spasm of muscles and as regards the incidence of lesions of the brain, cord, dura mater, nerve roots, muscles, fascia and ovaries.

Gross lesions of the brain and spinal cords of monkeys on cross section were rare, and microscopically small areas of necrosis and of leukocytic and round cell infiltration (fig. 7) with or without diplococci were seen occasionally. Grossly visible diffuse meningitis was not

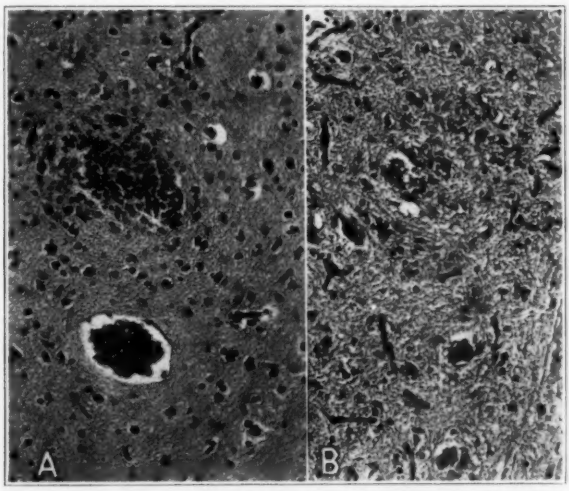

Fig. 7.—Areas of necrosis and cellular infiltration (*A*) in the brain and (*B*) in the medulla of a monkey inoculated five days previously with streptococci from the blood of a patient who had had recurring attacks of severe headache and severe deep-seated pain in the hips and legs. Hematoxylin and eosin stain; × 150.

encountered. The dura over the cerebral cortex and the calvarium was often seen to be extremely congested, and the dura covering the lumbar portion of the cord and the cauda, in addition to being congested, was often edematous, hemorrhagic and infiltrated (fig. 8). Both anterior and posterior nerve roots, especially in the lumbar region, were often extremely hyperemic, were surrounded by hemorrhage and edema and microscopically were seen to be infiltrated by leukocytes and round cells (fig. 9).

Fig. 8.—Edema, hemorrhage and cellular infiltration of the dura and nerve roots of the cauda of the monkey referred to in the legend to figure 7. Hematoxylin and eosin stain; × 50.

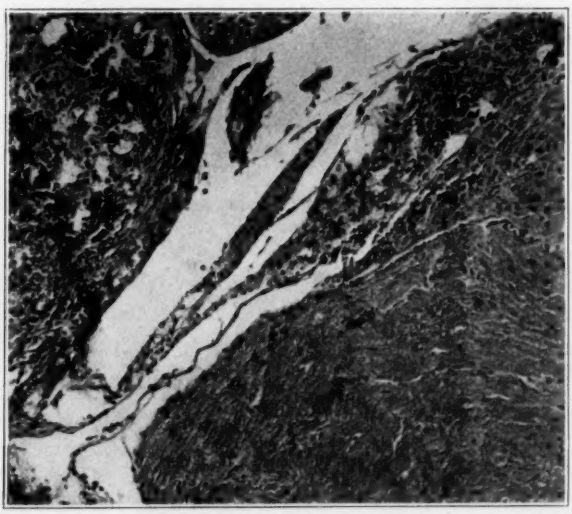

Fig. 9.—Edema and cellular infiltration of the nerve root and nerve sheaths in the lumbar region of the monkey referred to in the legends to figures 7 and 8. Hematoxylin and eosin stain; × 150.

Lesions caused by streptococci isolated from muscles, fascia and the urinary bladder are seen in figure 10. Especially marked were lesions surrounding nerves in the deep muscles of the lower region of the spinal column, in the psoas, in the muscles of the hip, upper parts of the thighs, thorax, posterior aspect of the lower end of the tibia and dorsa of wrists and ankles. The lesions consisted usually of relatively large areas of hemorrhagic infiltration occurring along fascial layers (fig. 10 *A* and *B*) and whitish necrotic areas in and between the muscle fibers. These were often numerous in one or in several muscles but were never widely disseminated among many muscles, as were those observed after similar injections of the streptococci of myasthenia gravis.[13] The microscopic

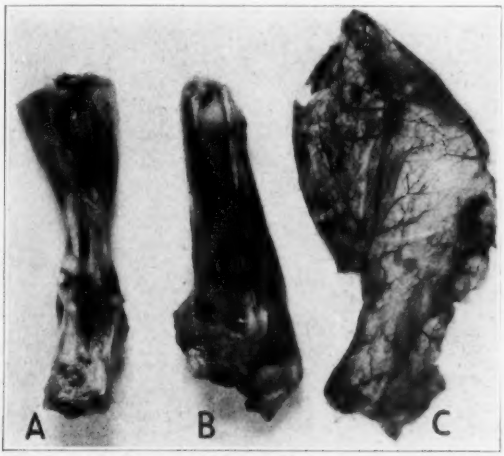

Fig. 10.—*A* and *B*, edema and hemorrhagic infiltration of the dorsum of the ankle joint and the anterior and lateral aspects of the tibia. *C*, hemorrhages in the urinary bladder of a rabbit inoculated intravenously with streptococci isolated from the stool. × ½.

lesions of the muscles consisted of edema and cellular infiltration of the interstitial tissue and of necrosis, degeneration and cellular infiltration of the muscle fibers (fig. 11). Lesions of the ovaries of animals given injections at the time of the epidemic of 1934 were not observed, but such lesions were found in 50 per cent of 35 female animals given injections during the present study. They occurred alike in rabbits and monkeys after injection of strains obtained from nasopharyngeal mucus, blood, spinal fluid, muscle and ovary and consisted of severe congestion,

13. Rosenow, E. C., and Heilman, F. R.: Bacteriologic Studies in Myasthenia Gravis, Proc. Soc. Exper. Biol. & Med. **34**:419-425 (May) 1936.

localized hemorrhages, edema, cellular infiltration and the presence of diplococci in tissue and cystic fluid (fig. 12). In almost all pregnant rabbits and mice after injection of the streptococci isolated in the present study abortion occurred.

Lesions of the lungs, of the mucous membrane of the trachea and of the gastrointestinal and urinary tracts (figs. 10 *C* and 13) were found in a relatively small number of animals given injections during the epidemic and somewhat later in the present study. Streptococci were isolated from excised pieces of muscle exhibiting lesions in 85 per cent of 33 animals (fig. 14 *A*) in the present study; from the brain (fig. 14 *B*) in 51 per cent and from the blood in 16 per cent of 60 animals

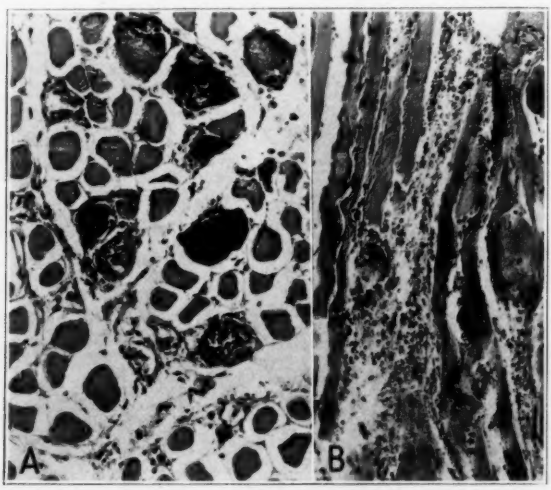

Fig. 11.—Edema, degeneration and cellular infiltration of the muscles of 2 rabbits (*A*) five days and (*B*) two days after intravenous injection of streptococci isolated from the spinal fluid. Hematoxylin and eosin stain; × 150.

given injections during the epidemic of 1934; from ovaries showing hemorrhage in 62 per cent of 16 female animals given injections during the present study (table 4; fig. 14 *C*) and from the brain in 46 per cent (fig. 14 *D*) and from the blood in 30 per cent of 77 animals inoculated during the present study. Control cultures from uninvolved tissues and blood of well animals never yielded streptococci.

In contrast, streptococci were not isolated from the muscles of any of 11 or from the ovaries of any of 9 animals given injections respectively of streptococci from well persons or of filtrates, sterile dextrose–

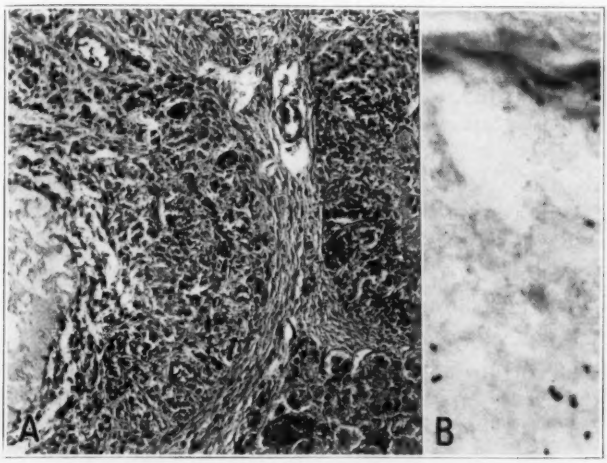

Fig. 12.—*A*, hemorrhage, necrosis and cellular infiltration in tissues and cellular infiltration in cystic fluid. *B*, diplococci in the ovary of a rabbit inoculated intravenously with streptococci isolated from the ovary referred to in the legend for figure 4. (*A*, hematoxylin and eosin stain, × 85; *B*, Rosenow-Gram stain, × 1,000).

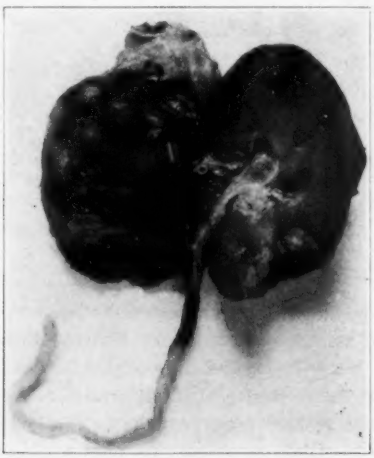

Fig. 13.—Subcapsular hemorrhage, infaretion of the kidney and hemorrhagic infiltration of the ureter of a monkey inoculated intraspinally and intracerebrally with a suspension in gelatin-Locke solution of the nasopharyngeal swabbings from 8 patients. × 1.

brain broth or saline solution. This striking difference in results in test animals and controls is in accord with results obtained in many other similar experiments. Filtrates of nasopharyngeal washings of patients with this bizarre type of disease were injected intracerebrally by standard methods for the detection of poliomyelitis and encephalitis viruses into rabbits, monkeys and mice. Virus "takes" were not obtained in a single instance.

During the present study 46 mice were given intracerebral or intraperitoneal injections of streptococci obtained from 27 patients. In some tremors and spasms associated with weakness (especially of the hind extremities) followed. Streptococci were isolated from the blood, pleural fluid or brain of 31 of the 42 mice that died.

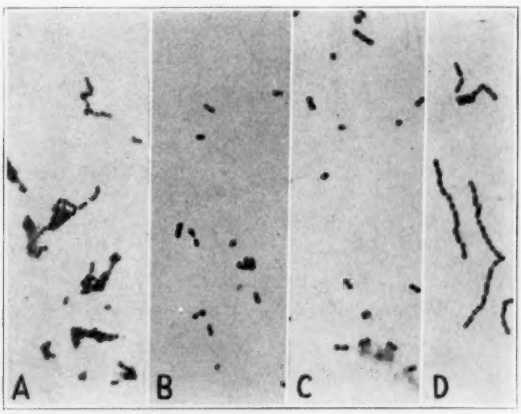

Fig. 14.—Streptococci isolated in dextrose–brain broth from (*A*) involved muscle of a monkey and (*B*) the brain of a monkey at the time of the epidemic of 1934 and (*C*) the ovary of a rabbit and (*D*) the brain of a monkey at the time of the present study, after intracerebral or intravenous injection. Gram stain; × 1,000.

The streptococci isolated from characteristic lesions produced by them in animals were grown in pure culture in dextrose–brain broth, and the cultures were filed away in hermetically sealed bottles. These cultures were kept at room temperature without transfer for about eighteen months. Subcultures yielded pure growths of the streptococci in many instances. The first subculture of each of four strains, from the blood, spinal fluid, muscle and ovary, respectively, was injected into rabbits in a manner similar to that used when the strain was first isolated. The animals showed lesions in the muscles, fasciae, dura, nerve roots, ovaries, stomach and urinary tract which resembled in type, distribution

and incidence those produced with the freshly isolated strains. An equal number of control animals given injections of streptococci freshly isolated from patients with colds and encephalitis exhibited no such lesions.

SPECIFIC LOCALIZATION OF STREPTOCOCCI FED TO ANIMALS

In order to determine the specific invasive power of the isolated streptococci with respect to the mucous membrane of the gastrointestinal tract, 12 mice and 12 rabbits were fed material containing the streptococci. As controls, 12 mice and 12 rabbits were given water sterilized with tincture of iodine (1:30,000). The suspensions of streptococci were prepared in such a manner as to contain approximately 2,000,000,000 organisms per cubic centimeter. The experiment was continued for one week, at the end of which all animals that had survived were etherized for examination. Three of the rabbits that received the suspensions died, but none of the mice that received the streptococci and none of the 24 controls died. Lesions were found in 9 of the 12 rabbits that were fed streptococci. They occurred chiefly in the dura mater, in and surrounding nerve roots (radiculitis), in muscles of the thighs, thorax and hips and in the peritoneum, uterus and ovaries. No lesions were observed in the 12 control rabbits. The streptococci were isolated from the brains of 3 of the 12 test rabbits, from the blood of 1, from the muscles of 7, from the peritoneal fluid of 9, from the kidneys of 5 and from the uteri and fetuses of 2 and the ovaries of 3 of the 5 females. In contrast, streptococci were isolated from only 1 of the 12 control rabbits and in that animal only from the liver. Of the 12 test mice which had received living streptococci, the organism was isolated from the livers of 4, from the spleens of 8, and from the ovaries of 5 of the 6 females in the group. In contrast, streptococci were isolated from the livers of only 2 and from the spleen of only 1 of the 12 controls. In no instance were streptococci isolated from the ovaries of the 4 females in this group.

PREPARATION AND USE OF STREPTOCOCCIC VACCINE

As soon as it was found that the streptococci isolated would produce lesions in animals similar to those observed in the patients from whom the organisms had been isolated, a composite vaccine was prepared from strains isolated from nasopharyngeal mucus, blood, spinal fluid and excised muscle. The organisms obtained in representative cases were grown for twenty-four hours in dextrose–brain broth, and the centrifuged bacteria were suspended densely in glycerin (2 parts) and 25 per cent solution of sodium chloride (1 part). This dense suspension was diluted in a solution of sodium chloride equivalent to the density of the

original culture (2,000,000,000 organisms per cubic centimeter). It was then heated to 75 C. (167 F.) for one hour. Sterility tests were made, and phenol to 0.2 per cent was added as a preservative. Extreme hypersensitivity to these organisms had been anticipated and was found to be present in most cases. Hence, the vaccine was diluted, tenfold, one hundredfold and one thousandfold, respectively, for use. In a few patients, who were only moderately sensitive, improvement, sometimes spectacular, followed the subcutaneous injection, at first twice and then once weekly, of gradually increasing doses of the vaccine. Most of those who were excessively sensitive either did not improve or were made worse by the vaccine.

COMMENT AND CONCLUSIONS

By means of special methods my associates and I have isolated the same type of streptococcus from the nasopharynx, stools and uterine cervix and, during exacerbations of the disease, consistently from catheterized urine, blood, spinal fluid, excised muscles and ovaries of patients suffering from recurring encephalomeningoradiculitis and fibromyositis. The common occurrence of infiltration of the dura, especially in the lumbar region, and the almost complete absence of cells in the spinal fluid, of animals given injections of the isolated streptococci indicate that the streptococci isolated from the spinal fluid were really from the infiltrated dura.

The almost simultaneous occurrence of exacerbations in many cases, the common presence of gastrointestinal symptoms in patients, the specific localization in animals after injection and feeding and the presence of the streptococci in large numbers in the stool during exacerbations of the disease indicate that the most probable source of infection in these cases was the gastrointestinal tract. Infection in teeth and tonsils seemed not to be the source in most of the cases.

The chief symptoms and lesions found in patients at the time of our study were reproduced in monkeys, rabbits and mice by intracerebral and intravenous injection and by feeding of the streptococci at the time of isolation and also eighteen months later. The findings referable to the ovaries recall the case of acute primary streptococcic ovaritis reported by Wilder.[14] The experimental production of ovaritis in animals by injecting streptococci isolated from ovarian tissues recalls the production of ovaritis electively by means of the streptococci isolated from ovaries undergoing sclerosis and cystic degeneration.[15] The lesions in nerve roots, fascia and muscles recall the results of similar studies of

14. Wilder, R. M.: Peritonitis Following Acute Ovaritis of Anginal Origin, J. A. M. A. **66**:569-571 (Feb. 19) 1916.

15. Rosenow and Davis, cited in footnote 10.

epidemic neuromyeloencephalitis,[16] neuromyositis or fibrositis,[17] myositis [18] and myasthenia gravis.[19]

On the basis of this experience I interpret the deep-seated pains in the back, hips and thighs and the weakness and undue fatigability so common to these patients as due chiefly to infection and intoxication of muscles (myositis), connective tissue (fibrositis), nerve roots (radiculitis) and dura mater (pachymeningitis). I interpret the extreme headache common to these patients as a toxic manifestation rather than as an indication of infection of the brain by the streptococci and infiltration of the dura mater due to the presence of the streptococci, and the extreme pain occurring during menstruation as referable to sclerosing infection of the ovaries.

The filtrable virus, as was to be expected, could not be demonstrated in nasopharyngeal washings and other suspected material, since enduring immunity to and disappearance of the virus occur regularly after frank and after abortive attacks of poliomyelitis in both human beings and monkeys. Immunity acquired during chronic streptococcic infections is of short duration; this seems to explain the recurring exacerbations and remissions which were such striking features of this group of cases. The widespread distribution and the character of the lesions and the extreme sensitiveness to the isolated streptococci and to the vaccine prepared from them may account for the fact that cure of the patients has been difficult.

The conclusion seems warranted, then, that this strange disease actually was not poliomyelitis at the time of our study but was, rather, encephalomeningoradiculitis of the type which is usually associated with fibromyositis, that it was caused by a type of streptococcus having simultaneous affinity in varying degrees for the nervous system, connective tissue, muscles and ovaries and, furthermore, that this type of streptococcus was related to that isolated by us during the epidemic of 1934.

Dr. Hugh T. Jones, of Los Angeles, suggested this study and assisted in the work. Drs. O. J. Sloan and E. T. Remmen, at the Physicians and Surgeons Hospital, Glendale, Calif., provided laboratory space and permitted clinical observations.

16. Rosenow, E. C.: Neuromyelo-Encephalitis During and Following an Epidemic of Hiccup: Diverse Localization of Streptococci, Arch. Neurol. & Psychiat. **16**:21-36 (July) 1926.

17. Rosenow and Jensen, cited in footnote 10.

18. Rosenow and Ashby, cited in footnote 10.

19. Rosenow, E. C., and Heilman, F. R.: Serologic Studies with Streptococci Isolated in Cases of Myasthenia Gravis, Proc. Soc. Exper. Biol. & Med. **34**:477-480 (May) 1936; footnote 13.

TUMORS OF THE ADRENAL GLANDS

I. A MODIFIED AIR INJECTION ROENTGEN TECHNIC FOR DEMONSTRATING CORTICAL AND MEDULLARY TUMORS

OLIVER COPE, M.D.
AND
RICHARD SCHATZKI, M.D.
BOSTON

The most important element in the diagnosis of an endocrine disease is the demonstration of an anatomically abnormal gland. Recognition of disorders of the thyroid, for example, has been facilitated by the ease with which the gland can be palpated in the neck or visualized by the roentgen rays if it is in the mediastinum. The presence of a tumor of the adrenal gland may not be demonstrable by palpation, displacement of the kidney or roentgen visualization unless the growth is of considerable size. Any method offering greater precision in the recognition of an adrenal tumor early in its history warrants further study. Perirenal insufflation of air at present yields the most promising diagnostic possibilities. Its technic forms the basis of this study.

There are three clinical syndromes associated with hyperfunctioning tumors of the adrenal cortex, namely, virilism, basophilism and (in the male) feminization. Recognition of these syndromes is easy when the disease is advanced or pronounced but difficult when it is early or mild. Confusion in the diagnosis is possible, since the signs of one syndrome may blend into those of another and since each syndrome may be simulated by disease originating in another gland. There is no infallible clinical or laboratory finding which points to the adrenal cortex as the primary source of the disease. For example, recent assays of the urine of the patient for androgen and estrogen are of limited diagnostic use, since the findings are not characteristic in cases in which the diagnosis is questionable and are definite only in cases in which it is clinically obvious. Demonstration of enlargement of the adrenal gland remains

From the Departments of Surgery and Medicine of the Harvard Medical School and from the Surgical Services and X-Ray Department of the Massachusetts General Hospital.

This study has been made possible by a surgical assignment to one of us (O. C.), through the cooperation of Drs. E. D. Churchill, A. W. Allen and J. V. Meigs of the Surgical Staff of this hospital.

the most reliable diagnostic measure in a case of suspected adrenal disease.

It may be difficult on a clinical basis to distinguish hyperadreninism due to a pheochromocytoma from other types of hypertension. With the progression of hyperadreninism permanent hypertension may develop, resembling other forms of essential hypertension, and the diagnosis is not made unless the patient is observed in a hypertensive crisis. A simple and safe method of visualizing retroperitoneal masses should prove useful in substantiating a clinical impression.

Of the methods commonly available for demonstration of enlargement of the adrenal gland, direct palpation of a tumor in the region of the gland has been the most reliable. The position of the adrenal gland under the dome of the diaphragm, in front of the tenth and eleventh ribs, makes direct palpation of the gland impossible unless it is considerably enlarged. Even at operation through the abdominal cavity, direct palpation of the gland may be misleading. Displacement of a kidney is only suggestive and does not occur to a degree detectable on physical examination unless the tumor is large. Pain from enlargement of the adrenal gland does not occur until either the tumor is massive or malignant extension has taken place. The normal adrenal gland cannot be identified by the ordinary flat roentgenogram. Unless a tumor of the gland has attained a certain size, simple roentgen visualization is not possible, and, as on physical examination, displacement or rotation of the kidney by a tumor above cannot be counted on unless the tumor has reached a diameter of at least 5 cm.

After the introduction of the roentgen rays, use was made of gases as contrast mediums in the peritoneal cavity.[1] Rosenstein [2a] and Carelli and Sordelli [3a] reported independently and almost simultaneously in 1921 improved visualization of the kidney by the retroperitoneal injec-

1. Rosenstein and others gave Rautenberg (Rautenberg, E.: Röentgenphotographie der Leber, der Milz und des Zwerchfells, Deutsche med. Wchnschr. **40**:1205, 1914) credit for the first pneumoperitoneum, although it had been used earlier (Lorey: Ueber eine Methode die Organe der Bauchhöhle im Röntgenbilde darzustellen, München. med. Wchnschr. **61**:274, 1914).

2. Rosenstein, P.: (*a*) Die "Pneumoradiographie des Nierenlagers," ein neues Verfahren zur radiographischen Darstellung der Nieren und ihrer Nachbarorgane (Nebenniere, Milz, Leber), Ztschr. f. Urol. **15**:447, 1921; (*b*) Erfahrungen mit der Pneumoradiographie des Nierenlagers, Med. Klin. **18**:529, 1922.

3. (*a*) Carelli, H. H., and Sordelli, E.: Un nuevo procedimiento para explorar el riñón, Rev. Asoc. méd. argent. **34**:424, 1921. (*b*) Carelli, H. H.: Sur le pneumopéritoine et sur une méthode personelle pour voir le rein sans pneumopéritoine, Bull. et mém. Soc. méd. d. hôp. de Paris **45**:1409, 1921; (*c*) El enfisema peri-renal en èl diagnóstico radiológico de las afecciones del riñón, Rev. Asoc. méd. argent. **36**:1127, 1923.

tion of oxygen or carbon dioxide. In both articles delineation of neighboring organs, including the adrenal glands, was described, but neither author suggested use of the method for demonstration of disease of any organ other than the kidney. Workers in different countries were prompt to explore the usefulness of the technic in cases of suspected renal disease. Following Rosenstein's lead, work was reported from Germany,[4] Finland [5] and Hungary.[6] Immediately after his initial report Carelli demonstrated his technic in France,[3b] Germany, England and the United States. Carelli's example stimulated interest, and minor modifications were suggested.[7]

Complications soon were encountered; mediastinal emphysema and air embolism were recorded. Although deaths from pneumoperitoneum had been reported,[8] no actual deaths from retroperitoneal perirenal insufflation of air were mentioned until recently.[9]

The first to point out the usefulness of perirenal retroperitoneal insufflation of air in the diagnosis of enlargement of the adrenal glands were Mosenthal [4b] and Löser and Israël.[4c] These three authors demonstrated roentgen hyperplasia of the adrenal glands after injection of gas in 2 sisters with virilism. The glands were not, however, proved diseased by operation or autopsy. The report of these cases was apparently lost sight of, and it was not until 1935, when Cahill [10] emphasized

4. (*a*) Boeminghaus, H.: Zur Pneumoradiographie des Nierenlagers, Ztschr. f. urol. Chir. **9**:51, 1922. (*b*) Mosenthal, A.: Unsere Erfahrungen mit der "Pneumoradiographie des Nierenlagers" nach P. Rosenstein, ibid. **12**:303, 1923. (*c*) Löser, A., and Israël, W.: Zur Pathologie und Diagnose des Pseudohermaphroditismus femininus externus als innerer Sekretionsstörung, ibid. **13**:75, 1923.

5. Jansson, C. G.: Beitrag zur Pneumoradiographie der Nieren, Acta chir. Scandinav. **58**:311, 1924.

6. Szabó, I.: Beiträge zur Pneumoradiographie, Beitr. z. klin. Chir. **129**: 677, 1923.

7. Chevassu and Maingot: A propos de l'insufflation péritonéale, J. d'urol. **13**: 54, 1922; L'inconstance des résultats fournis par l'insufflation périrénale, ibid. **13**: 118, 1922. Hernaman-Johnson, F.: The Carelli Method of Perirenal Inflation, Brit. M. J. **1**:91, 1922. Delherm and Laquerrière: La radiographie du rein par la méthode Carelli-Sordelli: Le pneumo-rein, Presse méd. **30**:133, 1922. Delherm, Laquerrière and Morel-Kahn: Sur un nouveau procédé d'exploration radiologique du rein: Le pneumo-péri-néphros, J. de radiol. et d'électrol. **6**:369, 1922. Quinby, W. C.: Perirenal Insufflation of Oxygen, J. Urol. **9**:13, 1923.

8. Case, J. T.: A Review of Three Years' Work and Articles on Pneumoperitoneum, Am. J. Roentgenol. **8**:714, 1921.

9. Fish, G. W., (*a*) in discussion on Roome, N. W.: Visualization of the Adrenal Glands by Air Injection, J. A. M. A. **112**:196 (Jan. 21) 1939; (*b*) personal communication to the authors.

10. Cahill, G. F.: Air Injections to Demonstrate the Adrenals by X-Ray, J. Urol. **34**:238, 1935. Cahill, G. F.; Loeb, R. F.; Kurzrok, R.; Stout, A. P., and Smith, F. M.: Adrenal Cortical Tumors, Surg., Gynec. & Obst. **62**:287, 1936. Cahill, G. F.: The Adrenogenital Syndrome and Adrenocortical Tumors, New England J. Med. **218**:803, 1938.

the advantages of retroperitoneal injection of air in disclosing tumors of the adrenal glands, that the procedure finally received the recognition it deserves.[11] Between the dates of publication of the paper by Löser and Israël and that by Cahill, seven papers appeared describing the use of retroperitoneal injection of gas.[12] In all of these papers only diseases of the kidney itself were considered, and with the development of improved pyelographic methods, the gas injection procedure fell into disuse.

Since the publication of Cahill's papers, Mencher,[13] Gianturco and Drenckhahn [14] and Roome [15] have added their recommendations of the procedure in the diagnosis of disease of the adrenal glands. In spite of these reports, Walters and Kepler [16] stated that they are unimpressed by the possibilities of the technic. In view of the possible hazards of the procedure, their skepticism is not without justification. Since all untoward effects are avoidable by use of the modified technic to be described in this paper, reconsideration of the procedure is necessary at this time in order that a useful technic shall not fall into disrepute.

The present study is based on 163 separate injections of air in 78 patients. In all of the cases studied there was some clinical reason to suspect disease of the adrenal glands. The size of the shadows outlined by air, visualized on the roentgen film, was confirmed by operative

11. Langeron and his associates demonstrated a large suprarenal tumor by intraperitoneal insufflation of air (Langeron, L.; Decherf, E., and Danes: Epithélioma cortico-surrénal avec virilisme et hirsutisme: Localisation par le pneumo-péritoine; extirpation chirurgicale, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:436, 1929). Because of the intervening peritoneum and renal fascia, air in the peritoneal cavity will not outline a normal adrenal gland or a small tumor of the gland.

12. Roseno, A., and Hartoch, H.: Das Pneumoradiogramm des Nierenlagers bei der Gallenblasendarstellung: Ein neuer Weg zu verfeinerter Diagnostik, Deutsche Ztschr. f. Chir. **198**:250, 1926. Schilling, H.: Pneumo-Radiography of the Kidney, Internat. Clin. **4**:138, 1927. Gottlieb, J.: Ueber Pneumoren, Ztschr. f. Urol. **21**:32, 1927. Dózsa, E.: Ueber die Indikation, diagnostische Bewertung und Gefahren der Pneumoradiographie, Ztschr. f. urol. Chir. **28**:365, 1929. Schüller, J.: Zur Frage des Skrotalemphysems nach Nierenoperationen, Ztschr. f. Urol. **24**:345, 1930. Viethen, H.: Technik und Indikationsstellung der Pneumoradiographie des Nierenlagers, ibid. **25**:1, 1931. Jansson.[5]

13. Mencher, W. H.: Perirenal Insufflation, J. A. M. A. **109**:1338 (Oct. 23) 1937.

14. Gianturco, C., and Drenckhahn, C. H.: The Rôle of Perirenal Injections of Gas in the Radiological Study of the Adrenal Glands, Radiology **30**:500, 1938.

15. Roome, N. W.: Visualization of the Adrenal Glands by Air Injection, J. A. M. A. **112**:196 (Jan. 21) 1939.

16. Walters, W., and Kepler, E. J.: Adrenal Cortical Tumors and Their Treatment: A Study of Seven Operated Cases, Ann. Surg. **107**:881, 1938.

exposure through a retroperitoneal approach [17] in 15 patients and by postmortem examination of 2 patients.

TECHNIC

Site of Injection.—The success of the air injection technic for visualization of the adrenal glands depends on the anatomic fact that the renal fascia, or fascia of Gerota, forms a compartment which encloses both the adrenal gland and the kidney. Air injected anywhere in this compartment diffuses throughout the perinephric fat, outlining the two organs into which the air does not penetrate.

The site of choice for injection of air into the perirenal space is the triangular fat pad below the kidney. The kidney is suspended partly by its vascular attachment, partly by fine bands of connective tissue running through the perinephric fat from the renal capsule to the renal fascia and partly by the pressure of the surrounding organs. The lower pole of the kidney rests in a mass of fat which lies between the anterior and posterior folds of renal fascia above the pelvic brim.

The presence of a ptotic kidney is first excluded by palpation or by roentgen examination. One per cent aqueous solution of procaine hydrochloride is injected into the skin with a fine needle just above the iliac crest, lateral to the semispinalis muscle (fig. 1). Two cubic centimeters of the procaine solution is then injected into the subcutaneous fat and external fascia, medial to the expected line of insertion of the needle. A 20 gage lumbar puncture needle with a stilet is passed through in the following order: the skin, the subcutaneous fat, the fused posterior and medial layers of the lumbodorsal fascia, the quadratis lumborum muscle in its lower and lateral portion, the anterior layer of the lumbodorsal fascia, the thin layer of paranephric fat and, finally, the posterior fold of the renal fascia, into the perinephric fat. After passing through the renal fascia the needle slips readily through the fat for 2 to 3 cm. until the anterior fold of the fascia is reached. Pushing the needle back and forth for 1 to 2 cm. in this space without encountering obstructing fascia is virtual anatomic proof of the position of the point.

With care and practice the needle can be felt to pass through each of these layers. As it is inserted the needle point passes not only anteriorly but slightly medially. In the route described the needle avoids the semispinalis and psoas muscles. If it is inserted too far medially it will penetrate the psoas muscle, and the distance traversed will have to be much greater before the perinephric space is reached. Also, the posterior leaf of the renal fascia thins out medially, and a less distinct

17. Cope, O.: Tumors of the Suprarenal Glands: III. Description of a Retroperitoneal Subdiaphragmatic Operative Approach to the Suprarenal Gland, to be published.

click is felt when the needle passes through it. Injection of the air behind the renal fascia, as in the peritoneal cavity, although it may outline a large tumor and the diaphragm, will not delineate the normal adrenal gland or a small mass.

When the needle is believed to be in place the stilet is withdrawn, a syringe containing the procaine is fitted and the plunger is withdrawn

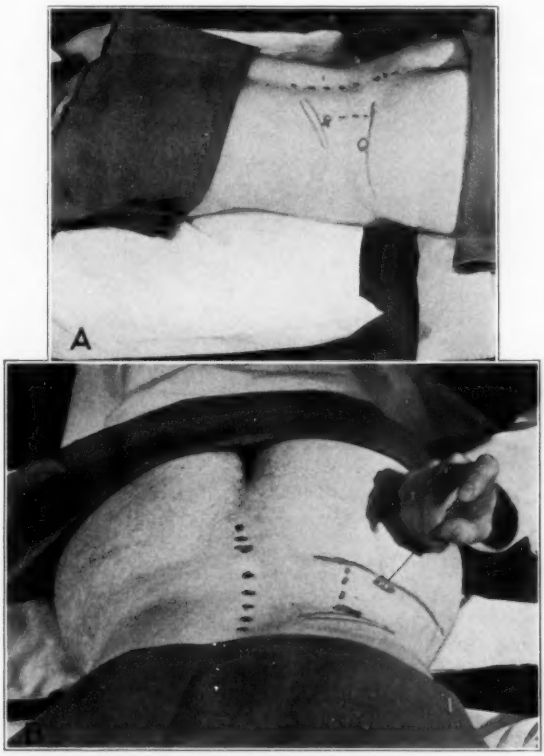

Fig. 1.—*A*, patient in position for injection on either side. A thin pillow is placed under the lower part of the chest and if necessary under the pelvis to obviate lumbar lordosis. The twelfth rib, the spinous processes, the crest of the ilium and the lateral border of the semispinalis muscle are marked. The circle indicates the optimal site of injection. The cross shows the usual but incorrect point of injection. *B*, closer view, taken from above the head of the patient, showing the angle of insertion of the needle in a patient of this build.

to make sure that the point is not within an aberrant vessel. Two cubic centimeters of the anesthetic solution is then injected. A second test of the position of the needle point is now possible; if the needle is still

in the muscle the solution enters only under pressure; if it is in fat tissue the solution runs in readily and can also be withdrawn. The syringe is now replaced by a glass adapter. This [18] is attached by rubber tubing to a second glass adapter, packed with sterile cotton, which in turn is connected to a 50 cc. tight-fitting ordinary syringe (fig. 2). A second withdrawal of the plunger is then advisable, and if the anesthetic solution and no blood returns, the injection of air is started.

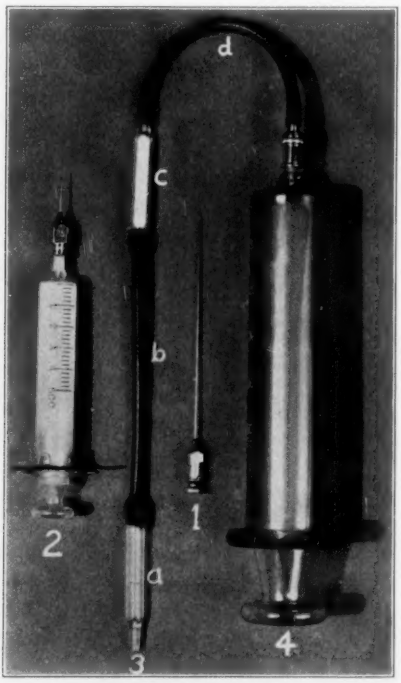

Fig. 2.—Paraphernalia required for injection of air. *1*, 20 gage lumbar puncture needle with stilet; *2*, 5 cc. syringe with a no. 25 needle; *3*, empty glass adapter (*a*), rubber tube (*b*), glass adapter packed with cotton (*c*) and connection rubber tubing (*d*). *4*, 50 cc. tight-fitting glass syringe. A clip or three way stopcock to close the rubber tubing while the syringe is being refilled with air is not needed, since the air is injected under low pressure. The rubber tubing may be closed between the fingers or left open.

Volume of Injection.—Two hundred cubic centimeters of air is ample for the adult; for a child smaller quantities are used. Larger volumes, although recommended by others, are unnecessary; the larger

18. More complicated apparatus is not necessary. A water manometer connected with the circuit is advisable while learning the procedure.

the volume, the greater the pressure required to complete the injection. Higher pressures increase the risk and the discomfort.

Rate of Injection and Pressure.—Not less than ten minutes is required to inject the air. The air as well as the anesthetic solution enters readily if the needle point is in the correct place. The pressure required for the injection of the air need never exceed 25 cm. of water; a pressure of 15 to 18 cm. usually suffices. Withdrawals of the plunger during the injection are wise. If the needle is in the right space, air will be recovered.

COMPLICATIONS

The technic used at this hospital has been particularly designed to avoid the following possible complications:

Air Embolism.—The most frequently reported complication of perirenal injection of air is air embolism. Except for the 2 deaths recorded by Fish,[9a] the reports in the literature have been of nonfatal embolism. A report, however, has come from another clinic of a recent death from air embolism authenticated by autopsy and by postmortem roentgen examination.[9b]

In injecting the air one is tempted to insert the needle point as near the gland as possible. In all accounts in the literature, exactly this procedure is recommended. In view of the vascularity of the region and of the adrenal gland itself, it is unwise to pass a needle into this area. Besides the three sets of vessels supplying the adrenal gland, the vessels to the other retroperitoneal organs, the pancreas, duodenum, spleen and kidneys, as well as the vena cava on the right side, must be considered. The aorta, with its pulsation and its thicker wall, is readily recognized and avoided. Penetration of any one of the veins may result not only in a hematoma but, on injection of the air, in embolism. In the anatomically well defined area recommended in this paper as the site of injection, only the minute vessels supplying the perinephric fat itself are present.

Besides the vascularity of the region, the rate of injection should play a role in the prevention of air embolism. If the needle is moved during the injection and the air enters a vein, the danger is minimized if the rate of injection is as slow as has been recommended. The 20 per cent of oxygen in the air is absorbed rapidly by the blood, and such nitrogen as is not absorbed immediately is found as small peripheral emboli in the lungs. To produce an embolus of sufficient size to cause circulatory embarrassment this volume of air would have to be injected much more rapidly.

The use of oxygen instead of air has been considered, since with its use there would be less danger of peripheral emboli in the lungs.

As will be pointed out under "Interpretation," however, many hours are sometimes required for proper diffusion of the gas, and oxygen is so rapidly absorbed from the tissues that good visualization of the adrenal glands would not always be obtained. The even more rapid absorption of carbon dioxide excludes the use of this gas in spite of its rapid rate of diffusion.

No signs or symptoms of air embolism occurred in the patients in this series.

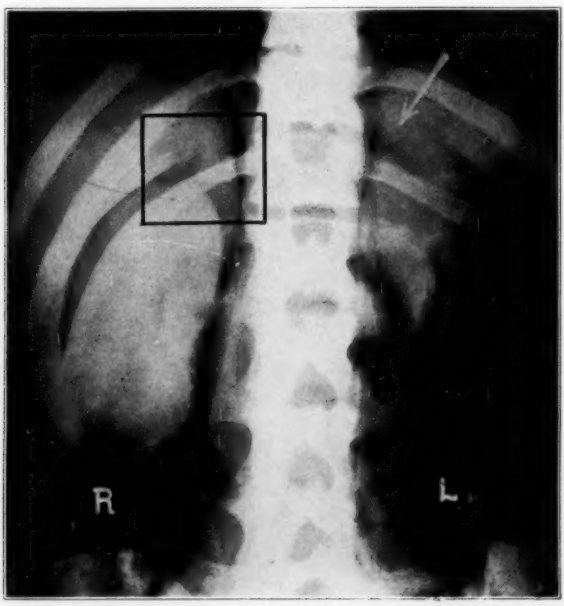

Fig. 3 (case 20).—Anteroposterior plate taken one-half hour after simultaneous bilateral periadrenal insufflation. A small mass, larger and denser than a normal adrenal gland, is seen occupying the right suprarenal space (see square). A normal adrenal gland is outlined on the left side (white arrow). The shadows of both kidneys are normal.

Hematoma of the Renal Capsule.—When the needle is inserted the kidney must be scrupulously avoided. In the twentieth case of this series the needle was felt to enter the capsule of the kidney. Blood oozed slowly from the needle. The needle was therefore withdrawn and inserted below the kidney, and the air was injected. The roentgenograms taken within one-half hour after the injection showed the outlines of a normal kidney (fig. 3). The films taken twenty-four hours later revealed an

enlarged, irregular, indistinct renal shadow (fig. 4). The patient, whose case has been reported elsewhere by Palmer and Castleman,[19] died six days later in one of her frequent hypertensive crises. At postmortem examination a large hematoma distending the true renal capsule and compressing but not involving the renal substance was found (fig. 5). Although it was undoubtedly not the direct cause of the death of this patient, a similar complication in another patient might well be the contributing or final cause of death. Had the hematoma been on the

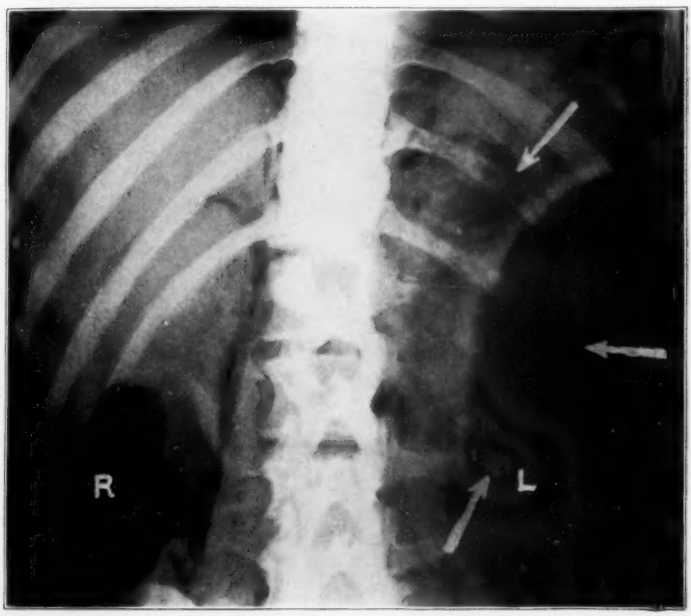

Fig. 4 (case 20).—Anteroposterior plate taken twenty-four hours after figure 3. The tumor of the right adrenal gland and the kidney are as previously outlined. The shadow of the left kidney is enlarged and irregular, with indistinct margins (white arrows). The shadow of the normal left adrenal gland is still visible. Compare with figures 3 and 6.

side of the pheochromocytoma a fatal outpouring of adrenin by direct pressure on the tumor might have occurred. The experience gained in this case emphasized the importance of introducing the needle into the perirenal space, well away from the kidney.

19. Palmer, R. S., and Castleman, B.: Paraganglioma (Chromaffinoma, Pheochromocytoma) of the Adrenal Gland Simulating Malignant Hypertension, New England J. Med. **219**:793, 1938.

Hematoma of the Adrenal Gland.—The fragility of the rich vascular network of the adrenal gland itself must be emphasized. Inconsiderate handling of the gland at operation may result in such rapid formation of a hematoma within the substance of the gland that an apparent tumor exists by the time the gland is completely exposed. We have seen elsewhere two normal glands removed because of such hematoma formation. Because of the delicate capsule and the paucity of supporting stroma a needle may easily be run through the adrenal gland without the operator being aware of it. A hematoma may occur as a result, and after the insufflation of air an apparent tumor, in reality the hematoma, may be

Fig. 5 (case 20).—Left kidney compressed by a hematoma within the true renal capsule, found at autopsy six days after a needle puncture wound. No hemorrhage is visible within the substance of the kidney.

outlined. Although this complication has not been met in this series of injections, the possibility of its occurrence is sufficient reason for introducing the needle at the site described.

Expression of Adrenin.—In the use of this technic in uncovering medullary tumors another point must be kept strictly in mind. Adrenin is readily expressed from such tumors, and sudden death has been reported from palpation of these tumors with discharge into the circulation of insupportable quantities of the secretion.[20] In a young woman

20. Howard, J. E., and Barker, W. H.: Paroxysmal Hypertension and Other Clinical Manifestations Associated with Benign Chromaffin Cell Tumors (Phaeochromocytomata), Bull. Johns Hopkins Hosp. **61**:371, 1937.

with a pheochromocytoma in this series, the worst attacks had followed increased abdominal pressure caused by her infant sitting on her abdomen. In injecting air care must be taken to avoid everything but minimum pressure. For this reason, obviously the smallest possible quantity of air should be used.

Pain.—Another reason for the low pressure and slow rate of injection of the air is the avoidance of pain. With the slow inflation of the perinephric space, at most a feeling of fulness is noticed deep in the flank or abdomen, comparable to the sensation of a distended stomach. Rapid injection of air may cause sharp pain. Although presumably this pain is produced by overdistention of the connective tissue spaces, actual rupture of the connective tissue must be considered. In 6 of the operative cases, exploration of the suprarenal and perinephric areas was done from three to thirty-eight days after injection of air. In none of the cases were there signs of rupture of any vessels. The 1 case in which there was any blood in the perinephric fat was the case in which a hematoma of the renal capsule was observed at autopsy. The blood presumably had oozed from the puncture wound in the renal capsule.[21]

Injection of air into the muscle layers results not only in an unsuccessful roentgen examination but in pain. In some of the earlier cases the injections were followed by considerable discomfort. In all of them air had infiltrated up through the psoas muscle, in some passing through the diaphragmatic crura into the mediastinum. When the latter occurred, some sensation of suffocation was noticed. In 2 cases air in twenty-four hours reached the neck, where it could readily be palpated. In none of the cases in which air was injected slowly and within the renal fascia was there undue discomfort or did the air pass above the diaphragm.

Fat Embolism.—Fat embolism has been suggested as a cause of death following injection of air. Although we are skeptical of the possibility of fat embolism under these circumstances, it cannot be dismissed on the available evidence.

INTERPRETATION

After the injection the patient is asked to walk around for at least half an hour. Massage of the loin, recommended by Cahill, has not been found necessary. Sometimes good delineation of the kidney and adrenal gland is obtained within a half hour. In the majority of cases more complete diffusion of the air and therefore better visualization of the organs is obtained after twenty-four hours. It has been the practice

21. At operation in 2 cases air was still present in the tissues. The presence of the air in no way presented an operative difficulty.

in all cases to take two sets of plates, one within an hour after the injection and the second twenty-four hours later. Anteroposterior and lateral views are taken each time. No special preparation of the gastrointestinal tract is necessary, but the colon should be clean. In order to obtain clearer lateral plates in the last 40 cases, air was injected on one side at a time except under special circumstances. One week is allowed to elapse between injections. In seven days practically all of the air has been absorbed. Dividing the examination into two parts has the added advantage of diminishing the feeling of distention.

The normal adrenal gland is not always visualized on the air injection roentgenograms. When outlined, in its variety of shapes it conforms closely to the gross anatomy of the adrenal gland as seen at operation or autopsy. The left gland is generally elongated; the right, pyramidal. In all cases in which suspected hyperplasia has been demonstrated at operation, a shadow corresponding to the operative finding has been visualized on the roentgenogram. One atrophied adrenal gland exposed at operation had not been visualized on any of the plates, and one normal gland, similarly verified, had been visualized on some but not all of the films.

A shadow representing an adrenal gland is identified on the roentgenogram by the preciseness of form and outline, the relative density and the position above the kidney. In none of the cases in which the diagnosis was verified has such a clearly defined mass not proved to be adrenal tissue. A difficulty in interpretation is caused by superimposed irregular shadows cast by the fat and connective tissue surrounding the gland. The density of the shadow cast by the normal gland is ordinarily greater than that cast by surrounding tissues but is less than that cast by the upper pole of the kidney.

The anteroposterior film gives the most satisfactory results, but lateral plates are advised as controls. Intravenous pyelographic studies have been made simultaneously with the air injection films in many cases. Since the injected air outlines the kidney so well, this procedure has not added anything to the knowledge of the adrenal gland.

USES

We have found periadrenal injection of air useful under the following circumstances:

1. Visualization of a small tumor not demonstrable by other means.

In figure 3 injected air is shown to have outlined a small tumor of the adrenal medulla. The tumor is recognized not only by its size and density, both of which are greater than those of the normal gland on the opposite side, but by the convex lateral and medial borders. The

tumor (fig. 6) was not visualized on the films taken for the intravenous pyelogram (fig. 7). The case is reported elsewhere.[19]

2. Exclusion of the adrenal glands as the primary source of disease by demonstration of normal shadows of these glands.

The syndromes sometimes associated with enlargement of the adrenal glands may be simulated, both clinically and in the laboratory findings, by disease elsewhere. Exclusion of disease of the adrenal glands by the

Fig. 6 (case 20).—Intravenous pyelogram before injection of air. The tumor of the adrenal gland is not identifiable, its mass not being sufficient to cast a separate shadow or to displace or rotate the right kidney.

demonstration of normal shadows helps to direct attention and, therefore, therapy to the proper site.

3. Demonstration of the presence or absence of a normal adrenal gland when a large tumor exists in the contralateral side.

The high mortality reported [16] as immediately following the removal of a tumor of the adrenal gland is due presumably to acute cortical insufficiency. The normal cortical tissue remaining after removal of the tumor is insufficient to supply the requirements of adrenal cortical hormone. The reported incidence of the absence of a normal gland in

the side opposite the tumor is thought to be due to atrophy from disuse of that normal gland. It is essential to demonstrate the existence of normal tissue before excision of a tumor, subtotal excision of the tumor being indicated if adequate normal tissue is not found. Demonstration by injection of air of a normal gland on the side opposite the tumor may preclude an operation, since satisfactory exposure of the adrenal glands is accomplished only through a posterior retroperitoneal approach,[17] necessitating a separate incision for exploration of each gland.

4. Visualization of bilateral hyperplasia of the adrenal glands.

Fig. 7 (case 20).—Tumor of the adrenal medulla, removed at autopsy from the right side. The body of the normal right adrenal cortex is shown on the superior and medial surface of the tumor.

The pathologic picture of hyperplasia of the adrenal cortex is not as yet on certain ground. All that can be said at present is that hyperplasia of the cortical layers may exist as a primary source of disease and that grossly the adrenal glands are enlarged in all diameters. The shadows cast by these enlarged glands with the air insufflation technic, although larger than those of the average normal gland, may be so nearly within normal limits that by the roentgen picture alone it may not be possible to make a diagnosis of cortical hyperplasia. In this field of adrenal cortical disease, therefore, the air injection technic is limited in its usefulness.

5. Differentiation of shadows mistaken for those of tumors of the adrenal glands.

Two patients have been referred to us in whose cases endocrine disease was suspected and flat roentgenograms had shown a shadow suggestive of tumor of the adrenal gland. In each case the error in interpretation was made apparent by the air insufflation technic.

COMMENT

Any procedure requiring insertion of a needle and injection of air is accompanied by some hazard. With the safeguards outlined, however, the procedure of periadrenal insufflation of air is a simple one which can be performed on an ambulatory patient. In the 163 separate injections there have been no fatalities and no signs of air embolism. The only complications occurred in the first 20 cases, in which the site of injection recommended in the literature was used. Besides the patient who had a hematoma of the kidney, there were 4 who had considerable discomfort. In each of these 4 air had escaped into the mediastinum owing to improper location of the needle outside the renal fascia.

In many of the articles in the literature advising modifications of the technic, statements are made that the needle should be passed so many centimeters in such and such a direction. The variation in anatomy of the individual patient is so great that such instructions are only misleading. To carry out the procedure properly surgical judgment is needed. Knowledge of the anatomy, although requisite, is not sufficient. Impetuosity, lack of precision and failure to check carefully the position of the needle will lead to complications and lack of success.

In spite of the safeguards the procedure is not recommended without reservation. It should be used only for patients in whose cases there is definite suspicion of disease of the adrenal glands. Its major use will be found in including or excluding the adrenal gland as the source of disease. It has been pointed out also that operative exploration of the uninvolved adrenal gland may be obviated by its use in the case of a patient known to have a tumor. Since the risk of periadrenal insufflation of air is less than that of direct operative exploration of a gland, the operative mortality rate for patients with disease of the adrenal glands should be lowered.

Except for the single cases reported by Mencher and Roome, the use of the technic reported in the literature has been limited to disorders of the adrenal cortex. Little attention has been paid to its applicability to adrenal medullary disease. There are two reasons, however, which make it more difficult to disclose a pheochromocytoma than a tumor of the cortex. In the first place, pheochromocytomas occur more often in medullary tissue outside the adrenal gland than do cortical tumors in ectopic cortical tissue. The air infiltration must, therefore, cover a

wider field of the retroperitoneal region. In the second place, the average size of the reported adrenin-secreting tumors is smaller. The possible hazard from the expression of adrenin from a pheochromocytoma during the injection of air is to be emphasized.

There will always be a limit to the amount of information which can be deduced from the roentgenograms, no matter how well the technical procedures of the air injection are completed. The absence of a suprarenal shadow, even though the distribution of the air in the perirenal space is adequate, does not necessarily mean that an adrenal gland is absent or atrophied. The presence of a shadow consistent with that cast by a normal gland cannot exclude absolutely the presence of a small tumor or of hyperplasia.

SUMMARY AND CONCLUSIONS

A modified technic for visualization of the adrenal glands by the injection of air into the renal space is described. In order to avoid complications, air is injected slowly, under low pressure, in small volume and into the lower rather than the upper portion of the renal space. The uses and limitations of the procedure as indicated by the results of 163 injections in 78 patients are discussed.

It is concluded that this procedure can be performed on ambulatory patients and without fatality if the proper safeguards are employed. It is an important adjunct in the inclusion or exclusion of disease of the adrenal gland, either cortical or medullary. By its use, not only can tumors be diagnosed earlier in the course of the disease but operative explorations of the adrenal glands can in certain cases be obviated. The mortality in the treatment of patients suspected of having disease of these glands will, therefore, be lower.

ELEVATION OF UREA NITROGEN CONTENT OF THE BLOOD FOLLOWING HEMATEMESIS OR MELENA

LEON SCHIFF, M.D.
AND
RICHARD J. STEVENS, M.D.*
WITH THE TECHNICAL ASSISTANCE OF ELLEN S. GARBER, M.S.
CINCINNATI

In the past few years a number of reports have appeared on the frequency and significance of azotemia following massive hemorrhage from the upper part of the digestive tract. The first of these communications were those of Sanguinetti [1] who in 1933 and 1934 reported elevation of the urea nitrogen content of the blood in 9 cases of gastric or duodenal ulcer with hemorrhage. He assumed that this increase was due chiefly to absorption of products of decomposition of the blood in the intestinal tract, resulting in a state of intoxication which might prove fatal. He actually recommended cecostomy in order to remove this blood. He reported significant elevation of urea in the blood of 2 of 3 persons fed pig's blood.

In 1935, Cristiansen [2] found elevation of the urea content of the blood and absence of urinary chlorides in 2 cases of bleeding gastric ulcer. He concluded that these changes were due to absorption of toxic substances resulting from bacterial decomposition of the blood in the intestinal tract in addition to a diminished supply of chorides in the diet. One of his patients showed no pathologic changes in the kidneys.

In the same year there appeared the reports of Sučić,[3] Ingegno [4] and Meyler.[5] Sučić reported elevation of the urea content of the blood

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* Justin A. Rollman Fellow in Internal Medicine, 1938-1939.

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From the Department of Internal Medicine, University of Cincinnati, and the Gastric Laboratory of the Cincinnati General Hospital.

1. Sanguinetti, L. V.: Curvas azohemicas en las hemorragias retenidas del tubo digestivo, Arch. argent. de enferm. d. ap. digest. y de la nutrición **9**:68-75, 1933; Azoemias en el curso de las hemorragias retenidas a nivel del tubo digestivo (estudio clinico y experimental), ibid. **9**:264-287, 1934.

2. Cristiansen, T.: Uraemia as Cause of Death in Massive Haemorrhage from Peptic Ulcer, Acta med. Scandinav. **85**:333-345, 1935.

3. Sučić, D.: Akute Azotämie bei grossen gastro-intestinalen Blutungen, Klin. Wchnschr. **14**:1316-1318, 1935.

(Footnotes continued on next page)

of 6 of 7 patients, 5 of whom had a duodenal ulcer, 1 a gastric ulcer and 1 cirrhosis of the liver. He fed 500 and 1,000 Gm. of calf's blood respectively to 2 patients and noted no increase in the urea content of the blood one and two days later. He reported no increase of this constituent in the blood of 5 patients with hemoptysis, in that of 2 persons subjected to relative starvation for three days or in that of 1 professional donor after venesection and removal of 600 cc. of blood. He concluded that the condition should not be ascribed to dehydration, because it can develop in spite of adequate administration of fluids.

Ingegno [4] found a value for blood urea of 38 mg. or more per hundred cubic centimeters in 17 of 42 cases of hemorrhage due to peptic ulcer. He stated that "the high nitrogen figures were found almost exclusively in those examined within three days of the acute episode" and that persistent or increasing elevation of the value for urea pointed to continuation of bleeding. There was no significant correlation between the degree of anemia and the azotemia. Like Sanguinetti, he concluded that the most significant factor in elevation of the urea content of the blood was the protein of the blood liberated in the gastrointestinal tract. He stated that such factors as hemorrhage per se, shock dehydration and starvation might also play a role. He reported normal concentration of blood chlorides in 5 cases and normal carbon dioxide–combining power of the blood in several cases, but gave no figures.

Meyler [5] noted elevation of the urea nitrogen content of the blood of 4 patients with bleeding peptic ulcer and concluded that the increase was due primarily to increased destruction of body protein associated with dehydration and starvation. He reported elevation of the blood chlorides of 2 patients and a normal concentration in the case of a third. In 1 instance he noted an increase in the indican content of the blood.

In 1936 there appeared Cristiansen's [6] second report, in addition to reports by Alsted,[7] Clausen [8] and Borst.[9] Cristiansen found eleva-

4. Ingegno, A. P.: Elevated Blood Urea of Acute Gastrointestinal Hemorrhage and Its Significance, Am. J. M. Sc. **190**:770-774, 1935.

5. Meyler, L.: Post-Haemorrhagic Uraemia, Acta med. Scandinav. **87**:313-325, 1935.

6. Cristiansen, T.: Hyperazotaemia in Intraintestinal Haemorrhage, Acta med. Scandinav., 1936, supp. 78, pp. 894-899.

7. Alsted, G.: Further Studies on Azotemia Following Hemorrhage in the Digestive Tract, Am. J. M. Sc. **192**:199-208, 1936.

8. Clausen, J.: Hyperazotemia in Cases of Acute Ventricle Hemorrhage, Acta med. Scandinav., 1936, supp. 78, pp. 908-914.

9. Borst, J. G. G.: Ueber Erhöhung des Kochsalz- und Harnstoffgehaltes und Erniedrigung des Albumingehaltes des Blutes bei Patienten mit starken Magenblutungen, Ztschr. f. klin. Med. **130**:74-96, 1936.

tion of the value for urea in 17 of 19 cases in which hemorrhage occurred and stated that the elevation may occur in cases of bleeding due to carcinoma as well as of bleeding due to peptic ulcer or to ruptured esophageal varix. He found that achloruria was not an essential accompaniment as he had at first thought and that the urea content of the blood decreased with the patient on a liberal diet without supplementary administration of sodium chloride. He concluded that the elevated value for urea does not necessarily indicate an unfavorable prognosis unless it persists, progresses or is complicated by achloruria. Later he [10] stated that the presence of blood in the intestinal tract is a prerequisite for the development of the azotemia, as no rise in the concentration of urea in the blood occurred when the blood was lost entirely through vomiting.

Alsted [7] reported an elevation in the value for blood urea of more than 39 mg. per hundred cubic centimeters in 22 of 26 patients suffering from hematemesis and melena. He found a depression of renal function in 1 patient in whose case the value for blood urea was 216 mg. per hundred cubic centimeters. This patient died four days after admission to the hospital, with uremic symptoms but "without any apparent organic renal affection." In 4 other cases in which the blood urea was increased there was no reduction of renal function.

Clausen [8] noted elevation of the value for blood urea in 3 patients with hematemesis within six to twenty-four hours after the occurrence of hemorrhage, followed by gradual disappearance of the azotemia in the course of a few days. He found no relation between the azotemia and the serum or urinary chlorides. In 2 of the cases in which there were no manifestations of shock, he reported what he interpreted as normal urea clearances; in a third, in which shock was present, he reported a "moderate reduction of the renal function (maximum clearance 29 cc., standard clearance 23 cc.) not sufficient to explain the azotemia." He permitted 500 to 600 cc. of ox blood to "infuse" into the stomachs of 2 patients and noted an increase in the blood urea of about 25 mg. per hundred cubic centimeters within eight hours, with beginning decrease at the end of twenty-four hours.

Borst [9] found elevation of the urea content of the blood in 5 of 6 patients with peptic ulcer and hematemesis. In 2 of the 5 patients the urea clearance was normal; in 2 others the reduction in clearance to 47 and 58 per cent was not sufficient to account for the increase in urea, whereas in the fifth case there was a reduction to 19 per cent. As there was simultaneous excretion of large amounts of urea in the urine, he felt that elevation of the urea content of the blood was due chiefly to increased breakdown of protein (derived presumably from the blood in the intestinal tract). Although there was a decided increase in the urea

10. Cristiansen, T.: Biochemical Changes in the Organism Produced by Massive Intra-Intestinal Hemorrhage, Rev. Gastroenterol. **4**:166-180, 1937.

content of the urine, the proportion of uric acid and creatinine was normal. He also reported increase of the indican content of the blood and of the urine, which he attributed to decomposition of the blood in the intestinal tract.

From the reports of these authors it will be seen that the elevation of the value for urea nitrogen [11] which frequently follows hematemesis or melena has been ascribed to a number of factors, namely, dehydration, shock, impairment of renal function, increased catabolism of body protein associated with starvation and absorption of products of decomposition of the blood liberated into the intestinal tract.

We have studied a series of 53 cases of hematemesis or melena observed with 1 exception [12] at the Cincinnati General Hospital since Oct. 1, 1937, paying particular attention to the concentration of urea nitrogen in the blood and its relation to clinical findings. In a small group of patients studies of renal function were made, which are to be reported separately. We have been able to confirm the observation that elevation of the urea nitrogen content of the blood following hematemesis may occur in the presence of normal renal function. Studies [13] have also been made after oral administration of citrated human blood which establish the importance of the quantity of blood present in the intestinal tract at a given time in the production of the increased value for urea nitrogen. In a number of instances the blood chlorides and the carbon dioxide–combining power of the blood were determined and found to be normal.

The determinations of the urea nitrogen content of the blood were carried out in duplicate on oxalated whole blood by means of the aeration method of Van Slyke and Cullen.[14] The specimens were obtained immediately after admission of the patient to the hospital before the administration of any food or fluid. In frequent instances the determinations were repeated once or twice daily until the urea nitrogen had returned to a level below 20 mg. per hundred cubic centimeters and had remained there for several days or more. Most of the specimens examined later than the day of admission were obtained under fasting conditions, although in some instances the blood was obtained shortly after a meal, usually breakfast. It was considered unnecessary to obtain all specimens under fasting conditions because of the fact that single meals con-

11. In some instances it was not clear whether the author was dealing with urea or urea nitrogen, as methods of determination were not given. Some of the very high figures probably refer to values for urea which are 2.14 times those for urea nitrogen.

12. Case 20 was observed at the C. R. Holmes Hospital.

13. Schiff, L., and others: Observations on Oral Administration of Citrated Blood in Man: Effects on Blood Urea Nitrogen, Am. J. Digest. Dis. **6**:597 (Nov.) 1939.

14. Van Slyke, D. D., and Cullen, G. E., in Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 547.

taining a usual amount of protein have only a minor effect on the concentration of urea in the blood (MacKay and MacKay [15]). According to Wu,[16] the urea nitrogen content of the blood plasma varies from 13 to 23 mg. per hundred cubic centimeters, with an average value of 19 mg. According to Berglund,[16] the normal values for whole blood range from 9 to 15 and for blood plasma from 10 to 17 mg. per hundred cubic centimeters. In a group of 9 controls, from whom blood was taken about two to three hours after a noon meal, we obtained values of 9.6 to 21 mg. per hundred cubic centimeters.

Immediately after admission to the hospital the patients were placed on a modified Meulengracht regimen similar to that used by Witts.[17] Fluids were freely administered either orally or parenterally. For the first two days the diet consisted of frequent feedings of eggnog, milk, cream, toast, pureed vegetables, strained orange juice, butter and water as desired. On the third day strained cereal, minced meat and baked or creamed fish were added.

The list of cases is given in table 1. In cases in which it is indicated, the cause of hemorrhage seemed reasonably established after clinical study, including roentgen examination, gastroscopic examination and occasionally esophagoscopic examination, biopsy or necropsy. It is seen that the value for urea nitrogen may be elevated in a variety of diseases producing hemorrhage from the esophagus, stomach or duodenum, as well as in cases of hemorrhage of undetermined cause.

A maximum value for urea nitrogen of 30 mg. per hundred cubic centimeters of blood or more was obtained in 36 cases (table 2). The maximum concentration was reached within twenty-four hours of the time of admission in most cases in which patients were seen within three days of the first observation of hemorrhage (table 3).

Elevation of the urea nitrogen content of the blood occurred in the absence of shock (chart 1). No shock was present in 6 of 15 cases in which the maximum concentration was 50 mg. per hundred cubic centimeters or higher, in 12 of 24 cases presenting a maximum value of 40 mg. or more, and in 22 of 36 cases with a level of 30 mg. or more. It should be noted, nevertheless, that shock was relatively more frequent in the cases in which the degree of nitrogen elevation was higher, as the figures just cited indicate. The criteria of shock were a systolic blood pressure of 90 mm. of mercury or less, tachycardia, sweating and pallor.

As the level of urea nitrogen in the blood was frequently observed to rise during hospitalization in the presence of adequate administration of fluid it is believed that dehydration can be excluded as an essential fac-

15. MacKay, E. M., and MacKay, L. L.: Concentration of Urea in the Blood of Normal Individuals, J. Clin. Investigation **4**:295-306, 1927.

16. Cited by Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 267.

17. Witts, L. J.: Haematemesis and Melaena, Brit. M. J. **1**:847-852, 1937.

TABLE 1.—*Fifty-Three Cases* of Hematemesis or Melena*

Case No.	Age of Patient	Sex of Patient	Probable Source of Hemorrhage	Day of Admission After Hemorrhage	Shock	Minimum R. B. C., Millions	Minimum Hb., Gm. per 100 Cc.	Maximum B. U. N., Mg. per 100 Cc.
1	65	M	Duod. Ulcer†	4	0	1.3	5.8	100
2	69	M	Duod. Ulcer†	1	0	1.5	7.8	48
3	65	M	Duod. Ulcer	2	0	3.0	9.3	38
4	55	M	Duod. Ulcer	1	0	1.7	6.2	40
5	50	M	Duod. Ulcer	1	+	1.7	5.2	56
6	56	M	Duod. Ulcer†	1	++	0.9	4.0	105
7	40	M	Duod. Ulcer	3	0	3.5	9.2	25
8	40	M	Duod. Ulcer‡	9	0	1.9	5.0	18
9	40	M	Duod. Ulcer‡	1	0	2.3	5.8	30
10	54	M	Duod. Ulcer	1	++	2.1	5.8	40
11	34	M	Duod. Ulcer	2	0	4.3	12.0	19
12	50	M	Duod. Ulcer	3	0	2.2	8.4	22
13	57	M	Duod. Ulcer†§	12	0	0.9	3.2	120
14	36	M	Duod. Ulcer	1	0	2.1	5.2	43
15	37	M	Duod. Ulcer	4	0	1.0	4.3	39
16	48	F	Duod. Ulcer	5	0	2.3	5.2	13
17	45	M	Duod. Ulcer	3	0	2.7	8.0	35
18	46	F	Duod. Ulcer‡	1	0	1.8	6.0	15
19	26	M	Duod. Ulcer‡	1	0	1.1	3.4	35
20	70	M	Duod. Ulcer	1	0	3.2	10.5	15
21	53	F	Duod. Ulcer	2	0	3.6	10.0	36
22	64	M	Gast. Ulcer	2	0	1.7	8.3	43
23	56	M	Gast. Ulcer	3	0	2.8	8.3	35
24	34	M	Gast. Ulcer	1	0	3.0	12.0	50
25	77	F	Gast. Ulcer	1	0	1.5	6.2	33
26	57	M	Hyp. Gastritis	1	++	2.1	9.2	64
27	54	M	Hyp. Gastritis	1	0	1.3	4.6	23
28	35	M	Hem. Gastritis†**	7	0	0.6	2.4	90
29	60	F	Gast. Neurinoma‡	1	0	2.8	7.0	37
30	41	F	Gast. Carcinoma‡	15	0	1.3	4.4	26
31	34	M	Gast. Lymphosarcoma‡	12	0	1.6	2.9	20
32	69	M	Esoph. Varix†	2	0	2.2	7.0	105
33	53	M	Esoph. Varix†	1	++	2.0	6.0	55
34	55	M	Esoph. Varix††	1	++	1.2	6.0	105
35	57	M	Ca. of pancreas eroding duod.†	1	++	1.3	3.0	50
36	33	M	Duod. Carcinoma†	14	0	1.8	5.2	11
37	26	M	Thrombocytopenic purpura	2	++	1.2	6.4	38
38	57	M	Ruptured aortic aneurysm†	3	0	1.9	8.6	14
39	31	F	Undetermined	1	0	2.5	6.8	29
40	52	M	Undetermined	1	+	0.9	3.5	40
41	77	M	Undetermined	1	++	3.3	9.0	36
42	42	M	Undetermined	2	0	3.8	13.0	46
43	62	M	Undetermined	3	+	1.0	4.6	43
44	29	M	Undetermined	2	0	0.8	4.0	37
45	65	F	Undetermined	8	0	2.2	6.0	15
46	52	M	Undetermined	1	0	3.4	12.0	38
47	53	M	Undetermined	3	+	1.1	4.8	56
48	36	M	Undetermined	4	+	1.7	5.2	23
49	50	M	Undetermined	1	+	2.1	6.5	65
50	65	F	Undetermined	1	+	1.1	3.6	60
51	24	F	Undetermined	2	0	2.2	8.2	23
52	79	M	Undetermined†	1	0	3.2	8.4	75
53	57	M	Undetermined	1	0	1.5	6.0	29

* The patients in cases 7 and 46 were readmitted to the hospital. Data on their cases after the second admission are given under the headings of cases 8 and 47 respectively.

† Necropsy performed.

‡ Operation performed.

§ Chronic nephritis; necropsy seven months later.

** Bacterial endocarditis.

†† Died—no autopsy performed.

tor in its increase. Two examples are given in chart 2. As the patients were adequately fed, the same would hold true for starvation.

There was no direct relation between the age of the patients and the degree of elevation of the urea content of the blood (chart 3).

A constant relation was not found between the concentration of urea nitrogen and the red blood cell counts. Some relation, however, is suggested between very high concentrations of urea and very low red cell counts, as in 5 of the 6 cases in which the value for urea nitrogen was 90 mg. or more per hundred cubic centimeters the red cell count was 1,300,000 or less (chart 4).

TABLE 2.—*Maximum Value for Blood Urea Nitrogen in Fifty-Three Cases of Hematemesis or Melena*

Blood Urea Nitrogen, Mg./100 Cc.	Number of Cases	Blood Urea Nitrogen, Mg./100 Cc.	Number of Cases
100 and above	5	40-49	8
70-99	2	30-39	13
60-69	3	Below 30	17
50-59	5		

TABLE 3—*Day of Maximum Elevation of the Value for Urea in the Blood of Patients Admitted to the Hospital Within Three Days of First Observation of Hemorrhage* *

	Maxmium Blood Urea Nitrogen (With reference to day after hemorrhage)			
	1st Day	2d Day	3d Day	4th Day
Admitted day of hemorrhage (21)	13	7	1	..
Admitted 2d day after hemorrhage (7)	..	2	2	3
Admitted 3d day after hemorrhage (4)	..	..	3	1

* The concentration of urea in the blood at the time of admission to the hospital was 30 mg. or more per hundred cubic centimeters.

Repeated determinations of the value for urea were made in the cases of 12 patients who recovered without signs of a second hemorrhage (chart 5). The rapidity with which the blood urea nitrogen may rise after hematemesis is illustrated by case 10. In this case the first hemorrhage occurred during hospitalization, the value for urea nitrogen rising from 21 mg. per hundred cubic centimeters twelve hours prior to the hematemesis to 40 mg. per hundred cubic centimeters five hours after the hemorrhage. In 6 cases in which the initial determination was made within the first twenty-four hours of bleeding, there was a rather sharp drop within the next twenty-four hours; in 4 there was a rise during the next twenty-four hours followed by a decrease. Whether this secondary rise was due to continued bleeding after admission to the hospital is not known.

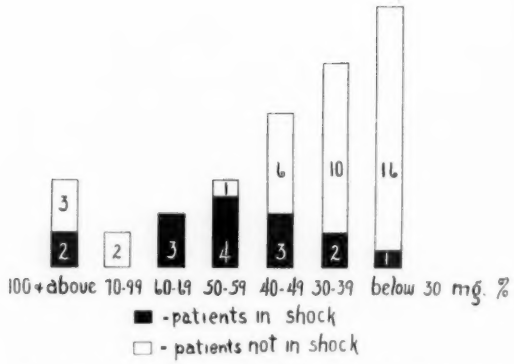

Chart 1.—Relation of shock to the maximum value for blood urea nitrogen.

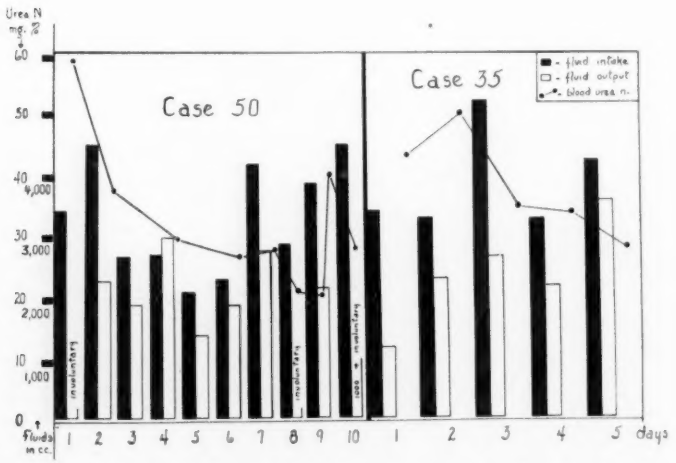

Chart 2.—Relation of the urea nitrogen content of the blood to fluid intake and output.

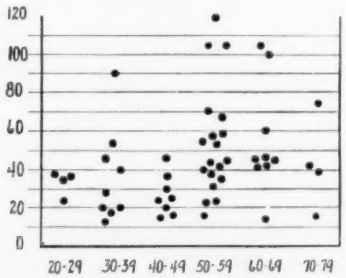

Chart 3.—Maximum value for urea nitrogen correlated with the age of the patient.

In 5 cases, in which the patients subsequently recovered, further bleeding occurred during observation in the hospital (chart 6), as manifested by hematemesis or by an episode of shock followed by the

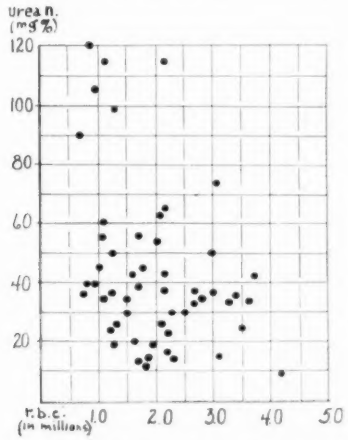

Chart 4.—Maximum values for urea nitrogen in the blood and coexistent red blood cell count.

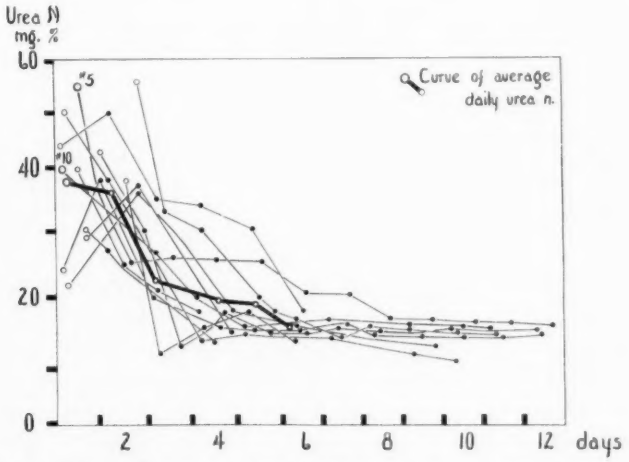

Chart 5.—Repeated determinations of the value for blood urea nitrogen in 12 cases of single hemorrhage followed by recovery.

passage of tarry stools. In 3 of these (cases 4, 43 and 50) there was a prompt rise in the urea nitrogen content of the blood followed by a rather prompt drop to normal by the third day after hemorrhage. In

case 17 the urea nitrogen, instead of dropping, remained at almost a constant level for one week, during which there were two episodes of bleeding. (There may have been additional occult hemorrhage.) In case 26 the value for urea nitrogen sixteen hours after the first hematemesis was 40 mg. per hundred cubic centimeters of blood. Five hours later a second hematemesis occurred. Three hours after this the value for urea nitrogen was 64 mg. per hundred cubic centimeters of blood, but it is likely that this increase was an aftermath of the first hemorrhage. It should be added that the urea nitrogen was elevated prior to the actual appearance of blood in cases 43 and 50, which suggests

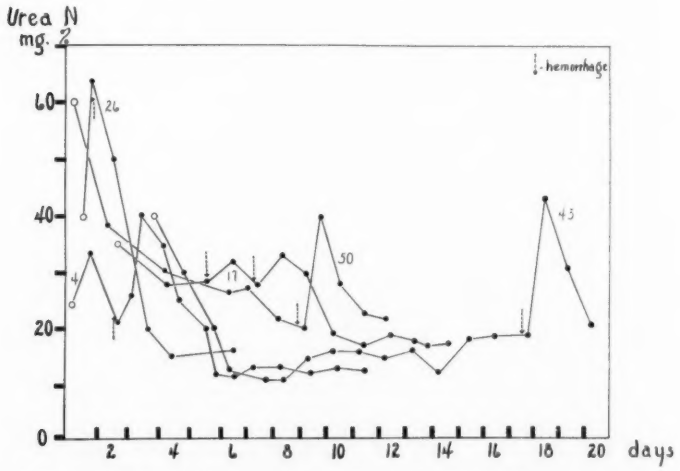

Chart 6.—Repeated determinations of the value for blood urea nitrogen in 5 cases of additional nonfatal hemorrhage after admission to the hospital.

that determination of the value should prove helpful in the early detection of gastrointestinal hemorrhage.

In 8 of the cases in which death occurred opportunity was afforded us to determine the concentration of urea nitrogen in the blood within the first three days of hemorrhage. The curves for 7 of the patients are shown in chart 7, the eighth having been excluded because death was due to postoperative pneumonia a month after admission. The highest values were obtained in 4 cases (cases 6, 32, 34 and 52); in all of these there was repeated hemorrhage, and varying amounts of blood were found in the gastrointestinal tract in the 3 in which autopsy was done. In case 2 there was also repeated hematemesis, yet the urea nitrogen content of the blood, though moderately elevated, decreased

somewhat before death, which occurred thirty-five hours after admission. In case 38, in which bleeding was due to an aortic aneurysm rupturing into the esophagus, a small hematemesis occurred two days before admission and was followed by profuse hematemesis on the day of admission as well as at the time of death, twenty-four hours later. There was practically no old blood in the intestinal tract, which suggested that almost all the blood lost the day before death had been vomited. In case 33, in which there was no bleeding after hospitalization, the urea nitrogen

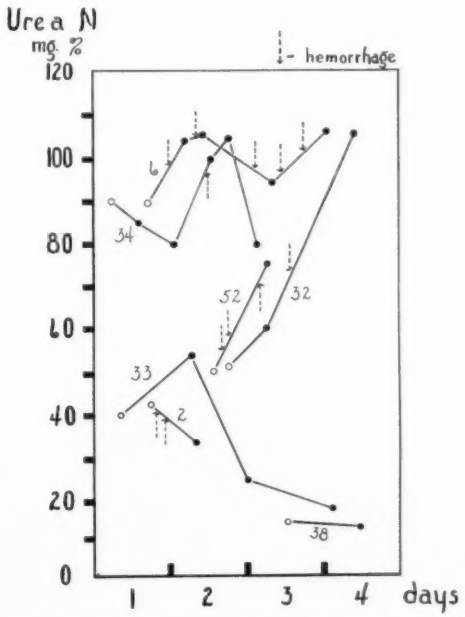

Chart 7.—Repeated blood urea nitrogen determinations in 7 cases of fatal hematemesis and melena.

curve resembled that seen in the cases of nonfatal single hemorrhage. Death in this case was probably due to hepatic insufficiency.

There was a definite relation between mortality and the degree of elevation of the value for urea nitrogen (table 4). If one excludes those cases in which the primary disease, rather than the hemorrhage it produced, was the cause of death (cases 28, 30, 35, 36 and 38), one finds a fatal outcome in 4 of 5 cases in which there was a value of 100 mg. or more, in 5 of 9 cases in which the value was 60 mg. or more and in no case in which there was a normal concentration.

It is believed by many that age is the most important single prognostic factor in cases of hematemesis or melena, the mortality of patients over 50 years old being much higher than that of patients below this limit. It is of interest, therefore, to note that in spite of its relation to mortality, there was no direct relation between the concentration of urea in the blood and the age of the patients, as has been indicated.

In view of its relation to mortality, we have, like Witts,[17] come to consider the level of urea nitrogen in the blood as a criterion for blood transfusion and have recently made it a rule to give transfusions in any case in which the value for urea nitrogen after admission rises to 50 mg. or more per hundred cubic centimeters of blood. This rule was followed in 9 cases; 6 of the patients recovered. Two of the 3 who died had hepatic cirrhosis.

TABLE 4.—*Maximum Values for Blood Urea Nitrogen and Mortality from Hemorrhage in Cases of Hematemesis or Melena (48 Cases*)*

Blood Urea Nitrogen, Mg./100 Cc.	Number of Cases	Number of Deaths	Blood Urea Nitrogen, Mg./100 Cc.	Number of Cases	Number of Deaths
100 and above	5	4	40-49	8	1
70-99	1	1	30-39	13	0
60-69	3	0	Below 30	14	0
50-59	4	1			

* Cases 28, 30, 35, 36 and 38 have been excluded because of the influence of the primary disease on mortality.

In 17 of the 53 cases the concentration of urea nitrogen in the blood was less than 30 mg. per hundred cubic centimeters. These cases, therefore, merit separate consideration. In 9 instances (cases 8, 16, 18, 30, 31, 36, 45, 48 and 51) the first determination was made on the fourth day after the hemorrhage or even later, so that a previous elevation may well have been missed. In 2 cases (39 and 53) the concentration of urea nitrogen might have been considered elevated, since the values in both were 29 mg. per hundred cubic centimeters. In 2 other cases (12 and 20) the blood might have been swept through the intestinal tract too rapidly to permit adequate absorption of its decomposition products, a result of a laxative taken at the time of hematemesis. In 1 instance (case 38), the case of ruptured aneurysm, there was no old blood in the intestinal tract. In 3 cases (7, 11 and 27) there was no explanation for the absence of a definite increase.

SUMMARY AND CONCLUSIONS

The urea nitrogen content of the blood is frequently elevated after hematemesis and melena, and the degree of elevation in such instances

is of definite prognostic significance. In cases in which there are a single hemorrhage and subsequent recovery this increase is generally maximal within twenty-four hours (occasionally within forty-eight hours) and is followed by a sharp drop to normal by the third day after bleeding. In cases in which there is a second (nonfatal) hemorrhage there is a secondary increase within twenty-four hours, with a drop to normal by the third day. In cases in which repeated hemorrhages occur and ultimately prove fatal there is an increasingly or persistently high level of urea nitrogen in the blood.

The elevation of the value for urea nitrogen in the blood following hematemesis and melena may occur independently of shock, starvation, dehydration or renal insufficiency. It is not directly related to the age of the patient or to the red blood cell count.

The urea nitrogen content of the blood should be repeatedly estimated in all cases of hematemesis or melena because of its prognostic significance. Its value in prognosis should, in turn, make it an aid to therapeutic management.

Dr. Sander Goodman gave clinical assistance with this work. The translation of Sanguinetti's communications was made by Dr. Louise Cockrell.

INTERCAPILLARY GLOMERULOSCLEROSIS

A SYNDROME OF DIABETES, HYPERTENSION AND ALBUMINURIA

ROBERT A. NEWBURGER, M.D.*
AND
JOHN P. PETERS, M.D.
NEW HAVEN, CONN.

In 1936, Kimmelstiel and Wilson [1] reported the pathologic observations in a group of 8 cases of a peculiar renal lesion to which they gave the name intercapillary glomerulosclerosis. On reviewing the clinical records of the cases they found that the observations fell into a fairly well defined symptom complex, consisting of diabetes, albuminuria, hypertension, retinal vascular changes, a more or less well developed nephrotic syndrome and some degree of renal insufficiency. Anson,[2] in 1938, published a study of the kidneys in the last 900 autopsies at the Hospital of the Medical College of Virginia; he observed 6 cases which satisfied the pathologic criteria proposed by Kimmelstiel and Wilson. Clinically the same features were present as in those of the latter workers, except that the nephrotic syndrome was present in only 2 instances. Neither of these groups of cases was completely studied medically, since a number of the patients were admitted to the surgical wards and others were moribund at the time of admission.

Similar cases have impressed us from the clinical standpoint as instances of peculiarly widespread degenerative vascular disease. In 4 such cases autopsy was performed; the 4 cases are reported in detail in this paper. These and 5 other cases, in which the presence of the lesions of intercapillary glomerulosclerosis was clinically suspected, are analyzed in succeeding paragraphs. Table 1 shows the frequency of the various features of the syndrome in our proved cases and in those of the authors cited.

REPORT OF CASES

CASE 1.—J. F., a 64 year old American housewife, was admitted to the surgical service Oct. 15, 1936 and discharged November 12. An adenocarcinoma of the

* Emanuel Libman Fellow.

From the Department of Internal Medicine, Yale University School of Medicine, and the Medical Service of the New Haven Hospital.

1. Kimmelstiel, P., and Wilson, C.: Intercapillary Lesions in the Glomeruli of the Kidney, Am. J. Path. **12**:83-98 (Jan.) 1936.

2. Anson, L. J.: Intercapillary Glomerulosclerosis, South. M. J. **31**:1272-1275 (Dec.) 1938.

right breast was found, and radical mastectomy was performed. The lymph nodes were not involved. Diabetes had been discovered fifteen years previously and had been controlled by means of diet, insulin being required for only a few weeks postoperatively. The systolic blood pressure ranged between 220 and 180, with the diastolic at 100. There was attenuation of the retinal vessels, and one small round hemorrhage was seen in the left retina. The heart was moderately enlarged to the left. There was no evidence of cardiac failure and no edema. The hemoglobin was 91 per cent. There were 4,200,000 erythrocytes per cubic millimeter of blood. Examination of the urine showed: specific gravity, 1.033; albumin, 3 plus, and sugar, complete reduction. The sediment contained occasional pus cells. The nonprotein nitrogen content of the blood was 24 mg. per hundred cubic centimeters. Roentgen examination of the chest revealed an enlarged left ventricle. The phenolsulfonphthalein excretion was 58 per cent in two hours.

TABLE 1.—*Frequency of Various Symptoms*

Symptoms	All Series (18 Cases)			Kimmelstiel (8 Cases)			Anson (6 Cases)			Present Group (4 Cases with Autopsy)		
	Examined	Found	Percentage	Examined	Found	Percentage	Examined	Found	Percentage	Examined	Found	Percentage
Diabetes	17	17	100	7	7	100	6	6	100	4	4	100
Albuminuria	17	17	100	7	7	100	6	6	100	4	4	100
Retinal changes	8	8	100	1	1	100	3	3	100	4	4	100
Hypertension	17	15	88	7	6	86	6	5*	83	4	4	100
Edema	18	15	83	8	7	88	6	4	67	4	3	75
NPN retention	14	11	79	6	5	83	4	3	75	4	3	75
Hyposthenuria (<1.020)	11	7	64	5	3†	60	3	2†	67	3	2	67
Hypoalbuminemia (<2.9%)	6	4	67	0	0	..	2	1	50	4	3§	75
Heart failure	18	6	33	8	4	50	6	1	13	4	1	25
Anemia	4	1	25	0	0	..	0	0	..	4	1	25

* The exception was a patient admitted in shock who never recovered.
† It is not stated whether sugar was present in concentration test specimens. Other patients, therefore, may also have had hyposthenuria.
§ Proteins not studied within a year of death in the third case.

The patient was readmitted to the hospital on Dec. 28, 1937. She had been treated in the outpatient department for gradually increasing edema which did not respond to digitalization and responded only temporarily to mercurial diuretics, ammonium chloride and urea. Despite a high protein diet the blood proteins fell from 5.15 per cent on May 6 to 4.68 per cent on admission.

Physical Examination.—The patient was chronically ill and wasted. She was moderately dyspneic but not orthopneic or cyanotic. No venous engorgement was noted. There was massive edema of the lower extremities and of the right arm. Blurring of the margins of the disks, retinal edema and narrowing and tortuosity of the vessels were present, as were many old and recent hemorrhages, some round and dark, others flame shaped and brighter red. The heart was enlarged to the left. The systolic blood pressure was 230 to 200, and the diastolic, 100. There was evidence of bilateral hydrothorax and of moderate ascites. The edge of the liver was palpated 2 to 4 cm. below the costal margin.

Laboratory Examination.—The hemoglobin was 77 per cent. There were 4,310,000 erythrocytes per cubic millimeter. Urinalysis showed: specific gravity,

1.024; albumin, 4 plus, and sugar, 0. The sediment contained occasional pus cells. The total protein content of the urine (Kjeldahl) was 13.2 Gm. per liter. The nonprotein nitrogen content of the blood was 47 and the sugar content (fasting) 135 mg. per hundred cubic centimeters.

Clinical Course.—The aforementioned diuretics were tried again, and thoracentesis was repeatedly performed, but no improvement occurred. Transfusions were given and a high protein diet was offered. The diet was not well taken by the patient, especially in the last four weeks, when anorexia was marked. The level of serum proteins fell to 3.06 per cent (albumin 1.23; globulin 1.70). The patient died of bronchopneumonia on March 16, 1938. One week before death the value for nonprotein nitrogen was only 48 mg. per hundred cubic centimeters of blood, and no uremic symptoms were present.

Necropsy.—The right kidney weighed 200 Gm. and the left 190 Gm. The thin, translucent capsule stripped with ease, the surface showing numerous small indentations. The cut surface showed thinning of the cortex with poor demarcation from the medulla. The pelvis and the ureter were not abnormal.

Microscopically, the fibrous capsule was thickened and moderately infiltrated by small round cells and plasma cells. Some glomeruli were completely hyalinized; practically all the others contained deposits of pink-staining hyaline material between the capillary loops. In many places this was seen to extend from the respective vas afferens or efferens in which the wall was hyalinized. Where the changes were most marked, the glomeruli consisted entirely of such hyalinized loops. The Bowman capsules were thickened in many places, with deposits of the same material, apparently, in layers beneath the epithelium. Adhesions between the hyalinized loops and the capsule were occasionally seen. The arteriolar walls were thickened, and in places the lumens were extremely narrow.

The pancreas and liver were not remarkable. Focal pneumonia was present. There was generalized arteriosclerosis.

Case 2.—V. L., a 56 year old Italian laborer, was first observed in the outpatient department on Jan. 18, 1928. He had diabetes known to be of two years' duration, which was poorly regulated. He complained that he had suffered from epigastric fulness and rare vomiting for an indefinite number of years. The systolic blood pressure was 160 and the diastolic 94. The radial arteries were thickened, and the achilles reflexes were absent. The urine contained a very slight trace of albumin and completely reduced Benedict's solution. The patient was advised to enter the hospital for study and regulation of the diabetes, but he did not return.

He was admitted to the hospital six years later. Since 1930 he had been treated for diabetes by a private physician, who placed him on a diet and prescribed 10 units of insulin twice a day. His weight had been maintained at 135 pounds (61 Kg.), but he complained of a return of epigastric discomfort for six months. During the two weeks prior to admission, vomiting had been frequent, and gastrointestinal roentgen series revealed marked pyloric obstruction. The systolic blood pressure was 170 and the diastolic 110. Many yellowish exudates were present in the ocular fundi, with increased light reflex of the vessels. The urine contained albumin (1 plus) but no cells or casts. The Kahn test of the serum gave a negative reaction. The nonprotein nitrogen content of the blood was 39 mg. per hundred cubic centimeters, the serum chlorides 96.8 milliequivalents per liter and the carbon dioxide content 74.8 volumes per cent. The value for total protein was 5.90 per cent (albumin 3.98, globulin 1.92), and that for serum cholesterol was 159 mg. per hundred cubic centimeters.

A partial gastrectomy was performed, after which the patient made an uneventful recovery. The surgical specimen showed a chronic peptic ulcer. The patient was discharged in good condition on Feb. 24, 1934.

He was readmitted to the hospital on Nov. 11, 1938. In another institution, where he spent five months in 1937 after a hemoptysis, tubercle bacilli had been found in the sputum. He made a good recovery and was discharged with a diagnosis of arrested pulmonary tuberculosis. During the summer and fall of 1938 he suffered repeated infections of the upper respiratory tract and increasing edema, which was only temporarily lessened by the administration of digitalis and urea.

Physical Examination.—The patient was wizened and chronically ill. He was lying flat in bed without dyspnea. There was considerable soft edema of all the extremities, the sacrum and the abdominal wall. The temperature, pulse rate and respiratory rate were normal. The blood pressure was 236 systolic and 124 diastolic. Examination of the fundi revealed normal disks, thinned, tortuous vessels with arteriovenous compression and numerous large and small yellowish exudates. One small splinter-like hemorrhage was present. The veins of the neck were not engorged. The lungs were hyperresonant except for dulness over the right base posteriorly. A few rales were heard at both bases. The heart was moderately enlarged to the left. The second aortic sound was tambour-like and split. The edge of the liver could be palpated just below the right costal margin. The prostate was diffusely enlarged to about twice the normal size. There was evidence of extensive peripheral neuronopathy in the lower extremities.

Laboratory Examination.—The hemoglobin was 78 per cent. There were 4,150,000 erythrocytes per cubic millimeter. Urinalysis showed: specific gravity, 1.010 to 1.016; albumin, 2 to 4 plus, and sugar, 0 to 2 plus. The sediment contained rare red blood cells and occasional hyaline and granular casts. The phenolsulfonphthalein excretion was 13 per cent in two hours. Analysis of the gastric contents revealed no free hydrochloric acid. The congo red test for amyloid disease gave a negative result. The circulation time (dehydrochloric acid, arm to tongue) was 18.5 seconds. The results of chemical examination of the blood are shown in table 2.

Clinical Course.—The patient was given a diet high in protein and free from salt. On a regimen of complete rest in bed, digitalis and urea solution, a prompt diuresis occurred. He lost altogether 15 pounds (6.8 Kg.) in body weight, and cleared up practically all of the edema. The nonprotein nitrogen content of the blood rose to 129 mg. per hundred cubic centimeters during administration of urea and though the level fell somewhat on withdrawal of the drug, it subsequently mounted again. The values for blood chlorides were high throughout, even when 20 Gm. of sodium bicarbonate was given daily for a period. General weakness became marked. Intercurrent bronchopneumonia further debilitated the patient. In his final week of life, frequent vomiting necessitated parenteral administration of fluid, by which an effort was made to maintain the electrolytes of the blood at the normal levels. The patient died in uremia on Jan. 28, 1939.

Necropsy.—The right kidney weighed 155 Gm. and the left 145 Gm. The capsule of each was translucent and streaked by dilated capillaries. The capsule stripped with some difficulty, leaving a finely granular surface, yellow-pink and slightly pockmarked. On section the kidney had a waxy, pale appearance. The cortex was thin, being no more than 5 to 6 mm. in maximum width. The linear cortical markings were almost obliterated, being replaced by irregular pink streaks and dots. The pelvis and ureter appeared normal.

Microscopically, the entire cortex was diffusely scarred by an increase in fibrous tissue. Practically all the glomeruli had undergone variable degrees of hyaline change. Some were completely hyalinized; others contained deposits of glassy, homogeneous pink hyaline material in smaller amounts, and this lay between the capillary loops. The more severely affected glomeruli had deposits of hyalin in the thickened outer cell layer of Bowman's capsule as well. The afferent arterioles in many instances possessed thickened and hyalinized walls with varying degrees of reduction in the calibers of their lumens. In general, there was thickening of the intima and media with encroachment on the lumens of the smaller arteries. Many of the tubules were collapsed, with patchy infiltrations of lymphocytes about

TABLE 2.—*Blood Chemistry (Case 2)*

Date	NPN, Mg./100 Cc.	Blood Sugar, Mg./100 Cc.	Serum Chlorides, Milliequivalents	Serum CO_2 Content, Volume per Cent	Serum Total Protein, Percentage	Serum Albumin, Percentage	Serum Globulin, Percentage	Comment
1938								
11/9	56	200	.....	....	4.66	2.91	1.75	In dispensary
11/17	129	...	.....	....	....	....	....	Urea medication; stopped 11/18
11/21	93	...	101.5	52.6	....	....	....	Phosphorus 5.66 mg. per 100 cc.
11/25	89	...	.....	....	....	....	....	
11/28	82	...	.....	....	5.28	3.90	1.88	Urine protein, 3.1 Gm. per liter, 7.1 Gm. per 24 hr.
12/7	102	...	105.7	42.5	5.15	3.26	1.89	
12/13	119	...	.....	....	....	....	....	
12/23	110	...	113.9	33.2	5.13	3.03	2.10	Added salt, 5 Gm. a day for 4 days
12/27	94	258	109	50.0	....	....	....	Sodium bicarbonate, 20 Gm. a day for 4 days
1939								
1/3	97	...	111.3	39.1	5.69	3.13	2.56	After transfusion of 525 cc. whole blood
1/9	106	...	.....	....	....	....	....	Urine protein, 2.5 Gm. per liter
1/17	113	...	105.8	27.6	5.20	3.15	2.05	Icteric index 7; parenteral fluids
1/23	142	...	105.4	21.7	....	....	....	

them. Some tubules were merely dilated, while in others there was evidence of cellular degeneration.

Generalized arterial and arteriolar sclerosis was present, with the most marked changes in the coronary and renal vessels. There was evidence of both old and recent cardiac infarctions. There was some focal pneumonia. With the exception of a moderate degree of hyalinization of the islets of Langerhans, neither the pancreas nor the liver was remarkable.

CASE 3.—S. D., a 69 year old American housewife, was first seen in the outpatient department in 1929, at which time diabetes was discovered and controlled by diet alone.

The first period of hospitalization was from May 10 to June 6, 1934. The patient complained of an ulcer on the right heel, of five months' duration. In addition to the local lesion, findings of note included a blood pressure of 150 systolic and

85 diastolic and sclerosis of the arteries of the retinas and extremities. The Kahn test for syphilis gave a negative result, there was no anemia, and the urine was free of albumin and formed elements.

The second period of hospitalization was from Oct. 20, 1936 to Feb. 18, 1937. Polyuria had been pronounced for three months, and several ulcers had appeared on the right foot in the previous three weeks. The blood pressure at this time was 195 systolic and 70 diastolic. The heart was moderately enlarged to the left. Pulsations were not felt in the arteries of the lower extremities. Examination of the urine showed: specific gravity, 1.014 (maximum); albumin, 2 plus, and sugar, 0. The sediment contained from 0 to 50 pus cells; culture yielded a growth of Bacillus coli. The nonprotein nitrogen content of the blood was 32 mg. per hundred cubic centimeters. The value for serum protein was 5.57 per cent (albumin 3.17; globulin 2.50). The ulcers healed very slowly. The amount of insulin required varied greatly. Occasional normal blood pressure readings were obtained.

The final admission was on Aug. 19, 1938. For the previous four months the patient had suffered from a slowly enlarging painful ulceration on the right fourth toe. For several weeks a crack in the thickened skin of the right great toe had been oozing and occasionally bleeding. During the previous winter she had had several attacks of weakness resulting in falls without loss of consciousness and with full recovery in a day or less on each occasion. For eighteen months increasing dependent edema was noted, largely clearing on rest in bed, and she also complained of diminishing vision, with "spots before the eyes."

Physical Examination.—The patient was well preserved. She was without dyspnea or other complaint except local pain in the foot. The fundi showed thinning and tortuosity of the arteries and rare deep hemorrhages. No exudates or blurring was noted. The systolic blood pressure was 205 and the diastolic 100. The heart was slightly enlarged to the left, with accentuation of the aortic second sound. A few rales were heard at the base of the right lung after cough. There was evidence of pulmonary emphysema. The edge of the liver was palpated 2 cm. below the right costal margin. The extremities were cool, and there was moderate edema of both legs and feet. Infected ulcers were present on the right foot, with beginning wet gangrene. Arterial pulsations could not be felt in the legs.

Laboratory Examination.—The hemoglobin was 95 per cent. There were 5,150,000 erythrocytes per cubic millimeter. Urinalysis showed: specific gravity, 1.012; albumin, 3 plus, and sugar, 0. The sediment contained 0 to 20 pus cells per high power field. The blood sugar was 165 and the nonprotein nitrogen 37 mg. per hundred cubic centimeters. The serum proteins were not studied.

Clinical Course.—The spread of gangrene and the presence of cellulitis and osteomyelitis of the toes necessitated midthigh amputation. Infection of the stump became uncontrollable, and the patient died Oct. 2, 1938.

Necropsy.—The right kidney weighed 130 Gm. and the left 115 Gm. The capsule was thin, stripping readily and revealing a slightly roughened, granular red-brown surface. The cut surface was gray-brown. The cortex was definitely narrowed, and the normal striations were dimly seen. The pelvis, calices and ureter were not abnormal.

Microscopic study revealed a thickened capsule with a moderate amount of round cell infiltration. Some glomeruli were completely hyalinized. Others contained a considerable quantity of pink-staining hyaline material replacing the

capillary loops. This material was also seen in the walls of the vasa afferentia and efferentia. Some glomeruli contained deposits of pink-staining hyalin between the capillaries. The smaller arteries were definitely thickened.

The pancreas and liver contained no notable lesions. There were a number of old and recent coronary occlusions with myocardial infarcts. The amputation wound was suppurative. Generalized arteriosclerosis was present.

CASE 4.—M. C., a 57 year old German housewife, was admitted to the hospital in February 1927, complaining of weakness of nine weeks' duration, for which she had consulted a physician, who discovered glycosuria and hypertension. Polydipsia had been present for two years, with slight polyuria and no nocturia. For the same period the patient had noted occasional numbness of the palms of both hands. Except for cough accompanying infrequent infections of the respiratory tract the past history and family history were not contributory.

Physical Examination.—The patient was flushed. She was in no distress, lying flat in bed without dyspnea. The temperature was 100.8 F., but the pulse rate and respiratory rate were normal. Slight blurring of the disks and moderate arteriosclerotic retinal changes were present. The tonsils were large, with some plugs of exudate in their crypts. A few rales and bronchovesicular breath sounds were heard over the region of the upper lobe of the right lung. The bases were clear. The heart was enlarged to the left, with regular rhythm and no murmurs. The systolic blood pressure varied from 210 to 154 and the diastolic from 120 to 90. There was no edema. The ankle jerks were not obtained.

Laboratory Examination.—The hemoglobin was 80 per cent. There were 5,200,000 erythrocytes per cubic millimeter. Examination of urine showed: specific gravity, 1.016 (maximum); albumin, 3 plus; sugar, 3 plus, and acetone, 0. The sediment contained an occasional hyaline cast. The Wassermann reaction was negative. The sugar content of the blood was 177 and the nonprotein nitrogen content 30 mg. per hundred cubic centimeters.

Clinical Course.—The diabetes was easily controlled by diet, with the addition for the first few days of 10 units of insulin. The thoracic signs persisted but never became more marked than on admission. The patient was afebrile except for a few days and was discharged after three weeks, much improved subjectively and with a gradual fall in the blood pressure to 152 systolic and 88 diastolic.

The second admission was in January 1932. In the intervening five years the vision had gradually failed. For two years the patient had gradually lost weight and strength, without definite symptoms. Eight weeks prior to admission there suddenly developed a productive cough and pain in the right side of the chest, and the patient vomited frequently. There was no fever. Glycosuria and diabetic symptoms were absent. There was almost continuous diarrhea, with six to ten watery stools daily throughout this period. Epigastric soreness was present for two days.

Physical Examination.—The patient was cachectic, dehydrated and pallid. The respirations were shallow but not rapid. The temperature was 97 F. and the pulse rate 90. The tongue was reddened and smooth. The pulmonary signs were those of extensive bilateral pneumonic involvement. The edge of the liver was firm and extended 3 cm. below the costal margin. Slight edema of the legs was noted. There were bilateral incipient cataracts, obscuring the fundi; on the left, however, a large organized hemorrhage could be seen.

Laboratory Examination.—The hemoglobin was 53 per cent. There were 3,200,000 erythrocytes and 5,700 leukocytes per cubic millimeter. The blood smear

gave evidence of hypochromic anemia. Examination of the urine showed albumin 4 plus and sugar 0. Examination of the sediment gave negative results. The sugar content of the blood was 129 and the nonprotein nitrogen content 58 mg. per hundred cubic centimeters. The total protein content of the serum was 4.94 per cent (albumin 2.34; globulin 2.60). The sputum contained many acid-fast bacilli. Roentgenograms of the lungs revealed extensive tuberculous infiltration, with a cavity in the upper lobe of the right lung.

Clinical Course.—The diarrhea responded to administration of camphorated tincture of opium U. S. P. Dehydration was combated by parenteral administration of fluids. Marked generalized edema promptly developed, persisting to the time of the patient's death in stupor three weeks after admission.

Necropsy.—Each kidney weighed 125 Gm. The capsule stripped with difficulty and revealed a granular yellow-brown surface. The cortex was of usual thickness and was yellow-brown as contrasted with the grayish medulla. The vessels stood out in cut section and were narrowed. A thrombus almost occluded the left renal vein. The pelvis and ureter were normal.

On microscopic examination the capsule was seen to be slightly thickened. A large number of glomeruli were seen to be composed of groups of hyaline deposits. Others contained only two or three capillary loops embedded in hyaline intercapillary material, while many other glomeruli had a few deposits of this material between the capillaries. The arterioles were moderately thickened. A small amount of amyloid was seen in a few glomeruli. It had not the distribution of the hyaline material described.

The pancreas was not unusual. The liver contained a few tubercles. There was extensive pulmonary and intestinal tuberculosis. Acute vegetative endocarditis was present on the aortic valve. There was a considerable degree of generalized arteriosclerosis.

PATHOLOGIC PICTURE

The kidneys in all 4 cases showed the typical lesions described by Kimmelstiel and Wilson.[1] Special staining methods were not applied to the sections except such as were necessary to disclose amyloid deposits. Many glomeruli in each case [3] were hyalinized completely (fig. 1) or in part, with the hyalin confined to the centers of the glomeruli or of the individual lobules (fig. 2). In this condition the number of capillaries of the involved glomeruli is apparently reduced; often but a ring of open capillaries surrounds the hyaline mass, which consists of a broadening of the intercapillary connective tissue, best seen at the hilus. A high degree of arteriosclerosis with fatty degeneration of the arterioles is present, in many cases overshadowing the specific lesions. The hyaline degeneration may be seen in some cases to extend from the vasa afferentia into the intraglomerular mass. The capillary walls are thickened. Those at the center seem to merge with the hyaline mass and collapse, their nuclei becoming embedded in the mass. They are seen to be in various stages of necrobiosis and may assume an onion peel arrangement about the central hyalin. The capsular changes consist of deposits

3. Except in case 2, in which fewer lesions were seen. Extensive vascular changes in the kidneys in this case masked the picture to some extent.

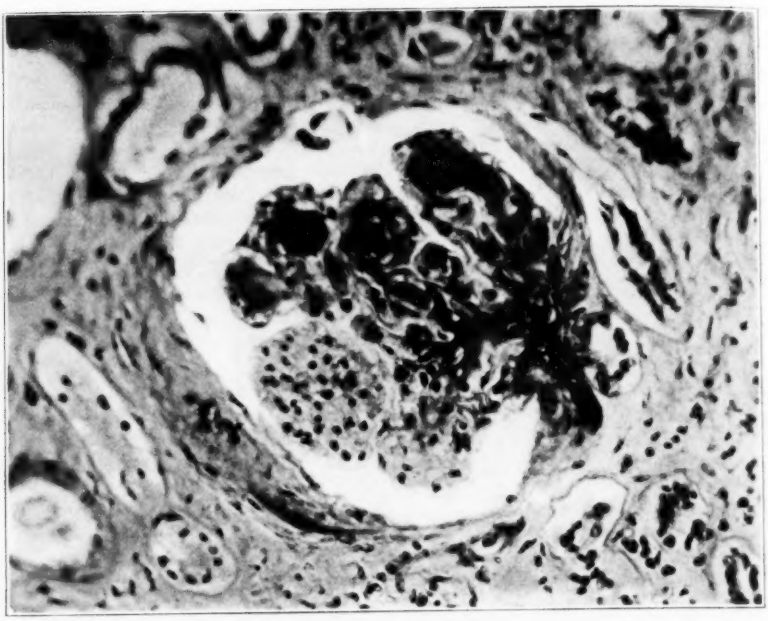

Fig. 1 (case 1).—A glomerulus partly involved. × 250.

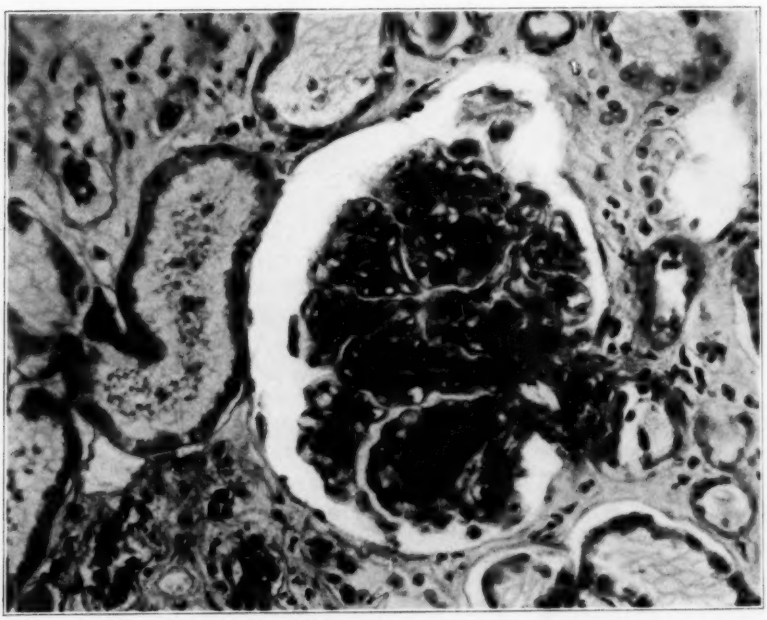

Fig. 2 (case 1).—A glomerulus markedly involved. × 250.

of hyaline material and lipoid beneath the epithelium. Kimmelstiel and Wilson have demonstrated by stains of the basement membrane that these deposits are laid down between the basement membrane and the epithelium. Tubular changes were inconstant, consisting mainly of fat deposits in the tubular epithelium. Nephrosclerotic changes were constantly present.

Kimmelstiel and Wilson pointed out the differences between the lesions described and those of intracapillary and of extracapillary glomerulonephritis. A stage exists in both these conditions in which similar lesions of the intercapillary connective tissue are observed. However, in these other types of glomerular disease, the marked changes in the basement membrane serve as the differential point.

CLINICAL FEATURES

The following discussion of the clinical phenomena associated with intercapillary glomerulosclerosis is based on our 4 cases in which autopsy was done and on 5 additional cases which were characteristic clinically. Two of the patients in the latter cases have died, but autopsies were not performed. The others are still living at the time of this report. Occasionally cases from the series collected by Kimmelstiel and Wilson [1] and by Anson [2] will be cited, but these are less useful for our purposes because of the sketchy nature of the case reports.

In general, it is of considerable interest that the patients presented many of the features of malignant hypertension (nephrosclerosis). The presence of hypertensive neuroretinopathy is stated by Fishberg [4] to be of ominous prognostic import, most patients with this symptom dying within a year. Even arteriosclerotic changes influence the prognosis unfavorably, although in diabetic persons this is of less significance. Profuse albuminuria, marked hypertension and evidence of renal decompensation individually would shorten the expectancy of life. Yet many patients have lived for a considerable period with most or all of these signs.

Age.—One patient in Anson's series was 35, but all the others of the combined groups were over 40 at the time of onset of the diabetes, albuminuria, or both.

Sex.—Of our 7 patients, 5 were women. Nine of the 16 others were women.

Diabetes.—This condition was present in all cases in the entire group and was not ruled out in the 1 exception in Kimmelstiel's group, in which the patient died before laboratory studies could be done. The

4. Fishberg, A. M.: Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, p. 694.

disorder was mild, usually requiring little or no insulin for control except when an infection supervened; in no instance did the diabetes appear to influence the progress of the disease. It is not unlikely that cases will be observed in which the diabetes is latent or even in which sugar tolerance is not decreased. Impairment of this function in patients with idiopathic hypertension, especially older persons, is well known.[5] Many of our patients have had hypertension at the time of discovery of the diabetes. One, however, who has had albuminuria and diabetes for sixteen years, had a normal blood pressure up to four years prior to the time of this report.

Albuminuria.—Albuminuria is considered an essential part of the syndrome and was present in varying degree in all cases. While it is usually profuse and is always so terminally, 1 patient had only a slight degree of albuminuria up to within a year of death, at which time a full-blown nephrotic syndrome developed. The early presence of albuminuria is of considerable significance from a diagnostic standpoint and may have a bearing on the pathogenesis of the disease.

Retinal Changes.—Arteriosclerotic changes in the retinas were present in all cases; in addition, papilledema, fresh hemorrhages and exudates characteristic of the malignant phase of hypertension were present in 5 instances. One patient had repeated hemorrhages and exudates in the macular regions, causing transient amauroses and progressive diminution of vision. Vision was seriously impaired by similar lesions in 2 other cases. Another patient, excluded from this series only because of the presence of a normal value for serum albumin, also went on to blindness owing to repeated retinal hemorrhages. Immature cataracts were present in 3 patients. It is of considerable interest that hypertensive changes, usually considered to be of ominous import, were present from two to five years in 4 of our patients who had these lesions.

Hypertension.—This condition was present for varying periods in all of the cases and was usually of considerable duration, being found on the first examination of all but 1 patient (the man mentioned previously, who had diabetes and albuminuria for sixteen years but hypertension for only four years). In 5 cases the systolic pressure exceeded 200 mm. of mercury; in 1 it exceeded 250. The presence of myocardial fibrosis due to coronary occlusion often results in a lowering of the blood pressure as it may have in 1 of Anson's cases. Patient M. C. (case 4) in our series had hypertension at the time of her first admission to the hospital, five years before death, and a normal blood pressure at a single examination in her final weeks, by which time extensive disseminated tuberculosis had developed.

5. Herrick, W. W.: Hypertension and Hyperglycemia, J. A. M. A. **81**: 1942-1944 (Dec. 8) 1923.

Edema.—Some degree of edema was present in the entire group and was well marked in 7 of the 9 cases. It was inversely proportional to the level of serum albumin, which in turn depended on the severity of the albuminuria and on the protein intake. In case 1, owing to a level of protein of 13.2 Gm. per liter of urine, there was a rapidly falling value for serum albumin in spite of a good protein intake.

Heart Failure.—Heart failure, when present, was mainly left sided, on a hypertensive basis; the heart failure on the right side was not proportional to the degree of edema. In 2 cases venous pressure and circulation time from the arm to the tongue were measured and found to be normal or only slightly elevated. Circulatory failure was the terminal event in 1 case.

Hyposthenuria and Nitrogen Retention.—These conditions were commonly found in our group, concentrating ability being moderately impaired in all cases and markedly so in 5; the nonprotein nitrogen content of the blood was elevated in all but 2 cases. None of our patients lived over a year with elevated values for nonprotein nitrogen, but there are too few cases in the series to warrant deductions as to the prognostic significance of nitrogen retention.

Anemia.—Hypochromic, normocytic or microcytic anemia was present in 4 of the patients, all of whom had nitrogen retention. The anemia, presumably on a renal basis, was characteristically unresponsive to iron therapy.

COMMENT

A consideration of the clinical findings and postmortem observations in a total of 18 cases presenting similar features and a characteristic lesion, together with 5 others without autopsy, seems to warrant grouping them together as falling into a distinctive disease picture, of which the constant features are diabetes, albuminuria, hypertension and retinal vascular changes. The nephrotic syndrome is common and depends for its development on the extent and duration of the albuminuria and the protein intake. Fishberg,[4] recognizing some of the clinical features of intercapillary glomerulosclerosis, emphasized the latter point.

The pathogenesis of this condition appears to depend on severe and extensive arterial and arteriolar degeneration, associated with and perhaps resulting in diabetes mellitus, hypertension and renal damage.

Differential diagnosis requires the exclusion of amyloid disease coincident with diabetes and hypertension, which rare combination might conceivably reproduce this syndrome. Patient M. C. (case 4) had slight amyloid changes in the kidneys and spleen, not sufficiently marked to account for the clinical picture. The nephrotic stage of chronic glomerulonephritis in association with diabetes usually occurs in a younger age group, and the history is often characteristic. In 1 case mentioned

by Kimmelstiel and Wilson but not included in their series, the picture was indistinguishable both clinically and pathologically from that of intercapillary glomerulosclerosis, since lesions both of the latter condition and of glomerulonephritis were present.

A search through the pathologic material of the New Haven Hospital revealed none of the characteristic renal lesions in 170 assorted cases, including cases of diabetes, hypertension, arteriosclerosis and various types of nephritis, with the exception of 1 case of subacute glomerulonephritis in a boy aged 14 who did not have diabetes or widespread vascular disease but who had a few suggestive intercapillary glomerular lesions. Special stains of the basement membrane were not done.

SUMMARY AND CONCLUSIONS

A group of 4 cases in which the lesions of intercapillary glomerulosclerosis were observed at autopsy is reported in detail, and the clinical findings in this and in two previously reported series are tabulated.

Five other cases in which intercapillary glomerulosclerosis was clinically suspected are analyzed.

The pathologic picture is described, and the reasons for considering intercapillary glomerulosclerosis a disease entity are discussed.

Dr. H. Arnold reviewed the pathologic material.

PHYSIOLOGIC BASIS OF INTRAVENOUS DEXTROSE THERAPY FOR DISEASES OF THE LIVER

SAMUEL SOSKIN, M.D.
AND
MAYER HYMAN, M.D.
CHICAGO

Since Rosenbaum,[1] in 1882, called attention to the depletion of hepatic glycogen following chloroform narcosis, arsenic or phosphorus poisoning and excessive administration of morphine, there has been adequate confirmation of the fact that a damaged liver contains little glycogen.[2] Concomitant with the loss of glycogen, fatty changes appear in the liver after exposure to these hepatotoxic agents. Rosenfeld[3] observed that animals fed carbohydrate are, in general, less susceptible to any drug which produces accumulations of fat in the liver. Furthermore, after such poisonings the feeding of dextrose aids recovery of the animal. Since the early reports of Whipple and Sperry,[4] Opie and Alford[5] and Graham[6] on the resistance to chloroform or phosphorus poisoning of animals fed large amounts of carbohydrate or animals with livers containing large stores of glycogen, there have been many

From the Department of Metabolism and Endocrinology, the Michael Reese Hospital.

1. Rosenbaum, F.: Untersuchungen über den Kohlehydratbestand des tierschen Organismus nach Vergiftung mit Arsenik Phosphor, Strychnin, Morphium, Chloroform, Arch. f. exper. Path. u. Pharmakol. **15**:450, 1882.

2. (*a*) Beddard, A. P.: A Suggestion for Treatment in Delayed Chloroform Poisoning, Lancet **1**:782, 1908. (*b*) Edie, E. S.; Moore, B., and Roaf, H. E.: Studies on Glycosuria, Biochem. J. **5**:325, 1911. (*c*) Macleod, J. J. R.: Studies in Experimental Glycosuria: IV. The Cause of the Hyperglycemia Produced by Asphyxia, Am. J. Physiol. **23**:278, 1908-1909. (*d*) Macleod, J. J. R., and Pearce, R. G.: Studies in Experimental Glycosuria: VI. The Distribution of Glycogen over the Liver Under Various Conditions; Post-Mortem Glycogenolysis, ibid. **27**:341, 1910-1911.

3. Rosenfeld, G.: Fettbildung, Ergebn. d. Physiol. **2**:50, 1903.

4. Whipple, G. H., and Sperry, J. A.: Chloroform Poisoning: Liver Necrosis and Repair, Bull. Johns Hopkins Hosp. **20**:278, 1909.

5. Opie, E. L., and Alford, L. B.: The Influence of Diet upon Necrosis Caused by Hepatic and Renal Poisons: I. Diet and the Hepatic Lesions of Chloroform, Phosphorus or Alcohol, J. Exper. Med. **21**:1, 1915.

6. Graham, E. A.: The Resistance of Pups to Late Chloroform Poisoning in Its Relation to Liver Glycogen, J. Exper. Med. **21**:185, 1915.

similar observations.[7] The protective action of high carbohydrate intake has also been noted in the prevention of hepatic damage following experimental ligation of the common bile duct,[8] operation for Eck fistula,[9] partial hepatectomy[10] and experimental poisoning with the mushroom Amanita phalloides.[11]

The various demonstrations of the life-saving action of high carbohydrate intake on animals with experimentally damaged livers have been paralleled by clinical explorations of the therapeutic and prophylactic possibilities of administration of dextrose to patients with diseases of the liver.[12] The earlier clinical work was lacking in striking results

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7. (*a*) Althausen, T. L.: Effects of the Administration of Glucose and Insulin on the Glycogen Content of Normal and Experimentally Damaged Livers, Ann. Int. Med. **6**:193, 1932. (*b*) Bollman, J. L.: Some Experimental Observations Pertinent to the Treatment of Hepatic Disease, ibid. **12**:1, 1938. (*c*) Davis, N. C., and Whipple, G. H.: The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, Arch. Int. Med. **23**:612 (May) 1919. (*d*) Moise, T. F., and Smith, A. H.: Diet and Tissue Growth: I. The Regeneration of Liver Tissue on Various Diets, J. Exper. Med. **40**:13, 1924. (*e*) Williamson, C. S., and Mann, F. C.: Studies on the Physiology of the Liver: V. The Hepatic Factor in Chloroform and Phosphorus Poisoning, Am. J. Physiol. **65**:267, 1923.

8. (*a*) Bollman, J. L.: Experimental Observations on Glucose as a Therapeutic Agent, S. Clin. North America **5**:871, 1925. (*b*) Bollman, J. L., and Mann, F. C.: Experimentally Produced Lesions of the Liver, Ann. Int. Med. **5**:699, 1931. (*c*) Ravdin, I. S.: Some Aspects of Carbohydrate Metabolism in Hepatic Disease, J. A. M. A. **93**:1193 (Oct. 19) 1929. (*d*) Mann, F. C.; Fishback, F. C.; Gay, J. G., and Green, G. F.: Experimental Pathology of the Liver, Arch. Path. **12**:787 (Nov.) 1931.

9. Hahn, M.; Massen, O.; Nencki, M., and Pawlow, J.: Die Eck'she Fistel zwischen der untern Hohlvene und der Pfortader und ihre Folgen für den Organismus, Arch. f. exper. Path. u. Pharmakol. **32**:161, 1893. Mann and others.[8d]

10. Stone, C. S., Jr.: Effect of Diet on Weight of Liver and Glycogen Concentration in Partially Hepatectomized Rats, Arch. Surg. **31**:662 (Oct.) 1935. Moise and Smith.[7d]

11. Steinbrinck, W.: Ueber klinische und experimentelle Beobachtungen der hypoglykämischen Reaktion bei Leberparenchymschädigungen, Klin. Wchnschr. **3**: 1029, 1924.

12. (*a*) Althausen, T. L.: Dextrose Therapy in Diseases of the Liver, J. A. M. A. **100**:1163 (April 15) 1933. (*b*) Baehr, G., and Klemperer, P.: Degenerative and Diffuse Inflammatory Diseases of the Liver, Internat. Clin. **2**:107, 1929. (*c*) Butt, H. R.: Common Emergencies Arising in the Course of Hepatic Disease, M. Clin. North America **22**:967, 1938. (*d*) Jacobi, H. G.: Glucose Tolerance as a Diagnostic Aid in Jaundice: III. Toxic Hepatitis, Am. J. Digest. Dis. & Nutrition **4**:162, 1938. (*e*) Jones, C. M.: The Treatment of Acute Hepatic Insufficiency and Its Relation to Prognosis, ibid. **3**:624, 1936. (*f*) Kehr, H.: Die gut und bösartigen Neubildungen der Gallenblase und der Gallengänge unter besonderer Berücksichtigung eigener Erfahrungen, Ergebn. d. Chir. u.

because of general failure to use sufficiently large amounts of carbohydrate. The recent experimental results obtained by Bollman and his co-workers have emphasized the therapeutic possibilities when adequate carbohydrate is administered.[13] On the basis of Rosenbaum's observations and Rosenfeld's theories, Beddard,[2a] as early as 1908, had suggested that dextrose be used clinically in large quantities to restore the depleted reserves of hepatic glycogen in cases of delayed poisoning after chloroform anesthesia. In addition to administration of dextrose by mouth and by rectal enemas, Beddard advised the clinical intravenous use of a 6 per cent solution. It is only recently, however, that the general introduction of adequate dextrose therapy for hepatic diseases has been shown to produce a definite decrease in mortality. In a series of cases in which acute hepatic insufficiency was treated with varying amounts of carbohydrate given by mouth and intravenously, Jones[12e] found that in a group of 10 cases observed from 1922 to 1925, in which the patients were given a diet low in fat and supposedly high in carbohydrate, the mortality was 90 per cent. In only 2 instances was dextrose administered intravenously. In the next five years, with diets somewhat higher in carbohydrates (300 to 400 Gm. daily) but with intravenous administration of dextrose in only 4 instances, there was 100 per cent mortality in 14 cases. However, in the years 1930 to 1935, when dextrose therapy was vigorous, 32 patients were treated with diets containing 400 to 500 Gm. of carbohydrate daily, 26 of them receiving dextrose intravenously and the mortality was lowered to 63 per cent. This author concluded: "The more intensive the glucose therapy, the better the prognosis."

This empiric finding has its rational basis in what is now known concerning the homeostatic mechanism of the liver. The work of Mann[14] and of Soskin[15] has shown that the liver is the sole source of the blood sugar. When the intact animal receives dextrose parenterally or via the gastrointestinal tract in sufficient amounts to raise the concentration of dextrose in the afferent hepatic blood above a definite threshold, the production of blood dextrose by the liver is suppressed. This mechanism was postulated by Soskin, Allweiss and

Orthop. **8**:471, 1914. (*g*) Snell, A. M.: The Treatment of Liver Disease, Ann. Int. Med. **12**:592, 1938. (*h*) Tallqvist, T. W.: Ueber die Beeinflussung des Eiweissumsatzes durch Fette und Kohlehydrate bei einigen Leberkrankheiten, Arch. f. Hyg. **65**:39, 1908. Beddard.[2a] Steinbrinck.[11]

13. Bollman, J. L.: Experimental Studies on Hepatic Alterations, Proc. Staff Meet., Mayo Clin. **11**:727, 1936; footnotes 7 *b* and 8 *a*. Bollman and Mann.[8b]

14. Mann, F. C.: The Effects of Complete and of Partial Removal of the Liver, Medicine **6**:419, 1927.

15. Soskin, S.: Muscle Glycogen as a Source of Blood Sugar, Am. J. Physiol., **81**:382, 1927.

Cohn [16] from a consideration of the concentration of dextrose in blood entering and leaving the liver during dextrose tolerance tests. It was substantially confirmed by Tsai and Yi [17] and later was directly demonstrated by Soskin and his co-workers,[18] who calculated the amount of sugar entering and leaving the liver with the aid of thermostromuhr measurements of blood flow. It was demonstrated also [16] that the response of the liver is not dependent on any extra secretion of insulin from the pancreas but is dependent on the presence of an optimal amount of circulating insulin. The decreased supply of sugar to the blood by the liver during hyperglycemia of exogenous origin is accompanied by an increase in the stores of hepatic glycogen. This hepatic mechanism for regulating the level of blood sugar has been compared to a thermostat-furnace combination.[19] In this analogy the room temperature is equivalent to the blood sugar level and the thermostat-furnace corresponds to the liver. With a sudden increase in the temperature of the room, the thermostat shuts the furnace off. The drop in the room temperature back to normal is chiefly due to the cessation of heat supply from the furnace, although some increase occurs in the dissipation of heat from the room. If on such an occasion one were to follow the room temperature closely one would see first a rise to and a little above the critical level of the thermostat, then a fall back to the previous constant level, with perhaps a little swing below normal, depending on the characteristics of the particular thermostat. This curve of rise and fall is analogous to the normal dextrose tolerance curve, when the influx of exogenous sugar into the blood stream causes the liver temporarily to cut off its supply of sugar to the blood.

There is evidence that one of the first effects of hepatotoxins is to act as irritants to the glycogenolytic mechanism of the liver.[20] To return to the analogy, the thermostat has been damaged and no longer reacts sensitively to its usual stimulus. Greater hyperglycemia, there-

16. Soskin, S.; Allweiss, M. D., and Cohn, D. J.: Influence of the Pancreas and the Liver upon the Dextrose Tolerance Curve, Am. J. Physiol. **109**:155, 1934.

17. Tsai, C., and Yi, C. L.: Carbohydrate Metabolism of the Liver: III. The Sugar Intake During Glucose Absorption, Chinese J. Physiol. **8**:273, 1934.

18. Soskin, S.; Essex, H. E.; Herrick, J. F., and Mann, F. C.: The Mechanism of Regulation of the Blood Sugar by the Liver, Am. J. Physiol. **124**:558, 1938.

19. Soskin, S.; Allweiss, M. D., and Mirsky, I. A.: (*a*) The Mechanism and Treatment of "Insulin Resistance" and Related Conditions, J. A. M. A. **108**:504 (Feb. 6) 1937; (*b*) Interpretation of Abnormal Dextrose Tolerance Curves Occurring in Toxemia in Terms of Liver Function, Arch. Int. Med. **56**:927 (Nov.) 1935.

20. Althausen, T. L., and Thoenes, E.: Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes: II. Phosphorus Poisoning, Arch. Int. Med. **50**:58 (July) 1932. Soskin and others.[19b]

fore, is necessary to suppress the supply of blood sugar and to favor deposition of glycogen in an acutely damaged liver than in a normal liver. However, when the blood sugar is raised to a sufficiently high level, the damaged liver does respond like the normal by ceasing to supply blood sugar.[21] The benefit derived from a decrease in the sugar-forming activity of the damaged liver may be regarded as equivalent to the favorable therapeutic results obtained by limiting the activity of other damaged tissues and organs in order to facilitate recovery and repair. The mechanism by which the "resting" or "splinted" liver is able to resist damage more effectively than the active or hyperactive liver is still unknown. The fact that many toxic substances are excreted as glycuronates [22] suggests that excessive stores of carbohydrate favor detoxification.

It is now generally accepted that acute and chronic destructive or degenerative processes of the hepatic parenchyma are best treated with large amounts of carbohydrate. A difference of opinion exists, however, concerning the advantages of intravenous administration of dextrose if the patient can take the necessary dextrose or carbohydrate by mouth.[23] The necessary amount of carbohydrate is supplied by the amount of dextrose sufficient to raise the blood sugar to a level which will suppress the output of hepatic sugar. Whereas the normal liver will respond to the usual postprandial hyperglycemia, the "irritable" liver associated with acute toxemia may require a much higher concentration of blood sugar to inhibit the formation of hepatic sugar. That this is so is seen in the prompt response of the acutely poisoned liver in curtailing its output of sugar when large doses of dextrose are given intravenously, small doses having little or no effect.[21] Furthermore, as Cori and Cori [24] have pointed out concerning the normal liver, "the blood sugar concentration and not the amount of glucose administered must be regarded as important for the rate of glycogen deposition in the liver." Consequently, when an attempt is made to protect a damaged liver by means of deposition of glycogen therein, the blood sugar concentration may have to be raised to a level which it may be impossible to obtain by feeding carbohydrates. In such a case intravenous infusion

21. Soskin, S., and Mirsky, I. A.: The Influence of Progressive Toxemic Liver Damage upon the Dextrose Tolerance Curve, Am. J. Physiol. **112**:649, 1935.

22. Sauer, J.: Die quantitative Glykuronsäuerbestimmung im Harn ist eine Leberfunktionsprüfung, Klin. Wchnschr. **9**:2351, 1930. Bollman.[8a]

23. Althausen, T. L., and Stockholm, M.: Deposition of Glycogen in Normal and in Experimentally Damaged Livers After Oral and Intravenous Administration of Dextrose, Am. J. Digest. Dis. & Nutrition **4**:752, 1938. Althausen.[12a] Snell.[12g]

24. Cori, C. F., and Cori, G. T.: The Influence of Insulin and Epinephrine on Glycogen Formation in the Liver, J. Biol. Chem. **85**:275, 1929-1930.

of dextrose is essential. The fact that extreme hyperglycemia so produced may result in glycosuria should not deter one from such vigorous therapy.

Because of the glycosuria which may result from intravenous dextrose therapy, some physicians favor the routine use of insulin with the sugar. However, it should be pointed out that unless the patient is diabetic the indiscriminate use of insulin may defeat the very purpose of the administration of dextrose. We have already referred to the evidence that in the presence of sufficient insulin to maintain a normal constant blood sugar level no additional insulin is necessary to obtain a normal hepatic response to administered sugar.[16] The injection of insulin into a nondiabetic person can, therefore, produce no additional hepatic effect but does cause increased storage of glycogen in the muscles. This peripheral effect causes a fall in the level of blood sugar, which in turn stimulates the liver to pour out more sugar. The liver is deprived of glycogen rather than replenished with it. Maintaining the hyperglycemia in spite of the administered insulin will prevent this reversal in effect but will not be more beneficial than the same amount of sugar without insulin. Soskin, Allweiss and Mirsky[19] have shown that the use of insulin with dextrose in the treatment of toxic nondiabetic animals shortens life; animals receiving dextrose alone live longer.

After prolonged intravenous injections of dextrose designed to suppress the sugar-producing mechanism of the liver, the organ requires an interval to recover from the inhibition of dextrose formation, so that hypoglycemia may appear one to three hours after the cessation of the infusion.[25] This should be anticipated and treated with small doses of carbohydrate given by mouth, or intravenously if necessary.

25. Soskin, S., and Allweiss, M. D.: The Hypoglycemic Phase of the Dextrose Tolerance Curve, Am. J. Physiol. **110**:4, 1934.

STUDIES ON DESTRUCTION OF RED BLOOD CELLS

I. CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: AN INVESTIGATION OF THE MECHANISM OF HEMOLYSIS, WITH OBSERVATIONS ON FIVE CASES

THOMAS HALE HAM, M.D.
BOSTON

The disease syndrome of chronic hemolytic anemia associated with paroxysmal nocturnal hemoglobinuria was described as a separate entity in 1928 and 1931 by Marchiafava [1] and in 1931 by Micheli.[2] The clinical manifestations have been reviewed recently with the report of cases by Witts [3] and by Hamburger and Bernstein.[4] The pathologic observations in 2 cases, with a review of the literature, were reported in 1938 by Scott, Robb-Smith and Scowen.[5] Van den Bergh [6] in 1911 made important observations on the in vitro manifestations of this disease without distinguishing it from acholuric hemolytic jaundice. A preliminary report on the mechanism of hemolysis was published in 1937 by Ham; [7] these observations were confirmed in 1938 by Dacie,

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

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1. Marchiafava, E.: Anemia emolitica con emosiderinuria perpetura, Policlinico (sez. med.) **35**:105, 1928; **38**:105, 1931.

2. Micheli, F.: Anemia (splenomegalia) emolitica con emoglobinuria-emosiderinuria tipo Marchiafava, Haematologica, I. Arch. **12**:101, 1931.

3. Witts, L. J.: Paroxysmal Haemoglobinurias, Lancet **2**:115, 1936.

4. Hamburger, L. P., and Bernstein, A.: Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, Am. J. M. Sc. **192**:301, 1936.

5. Scott, R. B.; Robb-Smith, A. H. T., and Scowen, E. F.: The Marchiafava-Micheli Syndrome of Nocturnal Haemoglobinuria with Haemolytic Anaemia, Quart. J. Med. **7**:95, 1938.

6. van den Bergh, A. A. H.: Ictère hémolytique avec crises hémoglobinuriques: Fragilité globulaire, Rev. de méd. **31**:63, 1911.

7. Ham, T. H.: Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria: A Study of the Mechanism of Hemolysis in Relation to Acid-Base Equilibrium, New England J. Med. **217**:915, 1937.

Israëls and Wilkinson.[8] Jordan[9] in 1938 published independent observations on the hemolytic mechanism.

The present communication deals with the relation of the acid-base equilibrium of blood to hemolysis in vivo and in vitro and with observations on certain features of the mechanism of destruction of red blood cells. Summaries are presented of the clinical and laboratory findings in 4 unreported cases, and observations on 1 case reported previously by Hamburger and Bernstein[4] are included. Another communication[9a] will deal with certain immunologic aspects of the hemolytic system in this disease.

MATERIAL AND METHOD

(*a*) *Quantitative Estimation of Hemoglobin in Plasma and in Urine.*—The benzidine method of Bing and Baker[10] was modified for the estimation of the concentration of hemoglobin in the plasma and in the urine. Venous blood was collected with a syringe and needle rinsed three times in 0.85 per cent sodium chloride solution and was then mixed with 10 per cent (by volume) of 3 per cent sodium citrate solution as an anticoagulant. To prevent hemolysis from manipulation of blood, only those samples were examined which were obtained by an uncomplicated venipuncture with a ready flow of blood. All samples were handled with a minimum of agitation. The specimen was centrifuged immediately, and the supernatant plasma was stored at ice box temperature. For estimation of hemoglobin, samples of from 0.05 to 0.2 cc. of plasma were introduced into 2 cc. of benzidine solution and the color reaction observed as described by Bing and Baker. The result was corrected for dilution of plasma by the anticoagulant. This method was sensitive and moderately accurate for concentration of hemoglobin as low as 20 mg. per hundred cubic centimeters of plasma. The concentration of hemoglobin in plasma from normal subjects collected with the aforementioned precautions was usually a trace and always less than 5 mg. per hundred cubic centimeters. A standard hemoglobin solution was prepared by diluting 1 cc. of venous blood to 2 liters with distilled water; the concentration of hemoglobin in the sample of venous blood was determined by the oxygen capacity method of Van Slyke.[11] Urine was collected daily in individual specimens under toluene and pooled for two periods of twelve hours each, the period from 9 p. m. through 9 a. m. representing the sleeping period and that from 9 a. m. through 9 p. m. the waking period. For estimation of the hemoglobin content, samples of 0.05 to 0.2 cc. of urine were added to 2 cc. of benzidine solution; the same volume of normal urine was added to the sample containing the hemoglobin standard.

8. Dacie, J. V.; Israëls, M. C. G., and Wilkinson, J. F.: Paroxysmal Nocturnal Haemoglobinuria of the Marchiafava Type, Lancet **1**:479, 1938.

9. Jordan, F. L. J.: Etudes sur l'hémoglobinurie, Acta med. Scandinav. **95**: 319, 1938.

9a. Ham, T. H., and Dingle, J. H.: Studies on Destruction of Red Blood Cells. II. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria: Certain Immunological Aspects of the Hemolytic Mechanism with Special Reference to Serum Complement, J. Clin. Investigation, to be published.

10. Bing, F. C., and Baker, R. W.: Determination of Hemoglobin in Minute Amounts of Blood by Wu's Method, J. Biol. Chem. **92**:589, 1931.

11. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

The addition of urine to benzidine caused variable precipitation of the reagent because of the salt concentration. This method as employed for urine, therefore, provided only a crude estimation of the hemoglobin concentration.

(*b*) *Hemolysis Test with Acidified Serum.*—The in vitro hemolysis test with acidified plasma or serum was performed on red blood cells washed three times in physiologic solution of sodium chloride and made to a 5 or 20 per cent suspension. Samples of 0.5 cc. of suspension were centrifuged in tubes 9.5 cm. in length and 0.9 cm. in internal diameter, and the supernatant salt was discarded. To the packed cells were added 0.5 cc. samples of serum or plasma. The plasma contained as anticoagulant heparin, in 15 per cent solution in distilled water, in a concentration of 130 mg. per one hundred cubic centimeters of whole blood; routinely, serum and erythrocytes were obtained from defibrinated blood. The suspension was acidified by equilibration with mixtures of oxygen and carbon dioxide at room temperature or by the addition to plasma or to serum of 5 per cent (by volume) of certain acids, e. g., 0.85 normal lactic acid or ⅓ normal hydrochloric acid (see section 6). The suspensions containing acidified serum were then incubated for from one to two hours at 37 C. and centrifuged. The percentage increase of hemolysis was estimated by determining the hemoglobin content of the serum or plasma compared with 100 per cent hemolysis produced by distilled water.

(*c*.) *Blood p_H; Blood Gases.*—The determinations of the p_H of blood by the glass electrode method [12] and of the carbon dioxide and the oxygen content of blood [11] were performed on samples of arterial blood kept at 0 C., containing 130 mg. of heparin per hundred cubic centimeters of blood.

(*d*.) *Other Determinations.*—The methods of estimation of the formed elements of the blood,[13] the serum bilirubin,[14] the platelets,[15] the clotting time,[16] the plasma proteins,[17] the Donath-Landsteiner reaction,[18] the resistance of the red blood cells to hypotonic saline solution,[19] the hemosiderin content of the urine and [20] the

12. Dill, D. B.; Daly, C., and Forbes, W. H.: The p_H of Serum and Red Cells, J. Biol. Chem. **117**:569, 1937.

13. Wintrobe, M. M.: Macroscopic Examination of the Blood, Am. J. M. Sc. **185**:58, 1933.

14. Barron, E. S. G.: Bilirubinemia, Medicine **10**:77, 1931.

15. Pohle, F. J.: The Blood Platelet Count in Relation to the Menstrual Cycle in Normal Women, Am. J. M. Sc. **197**:40, 1939.

16. Pohle, F. J., and Taylor, F. H. L.: The Coagulation Defect in Hemophilia: The Effect in Hemophilia of Intramuscular Administration of a Globulin Substance Derived from Normal Human Plasma, J. Clin. Investigation **16**:741, 1937.

17. Ham, T. H., and Curtis, F. C.: Plasma Fibrinogen Response in Man: Influence of the Nutritional State, Induced Hyperpyrexia, Infectious Disease and Liver Damage, Medicine **17**:413, 1938.

18. MacKenzie, G. M.: Paroxysmal Hemoglobinuria, Medicine **8**:159, 1929.

19. Daland, G. A., and Worthley, K.: The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride, J. Lab. & Clin. Med. **20**:1122, 1935.

20. Cook, S. F.: Structure and Composition of Hemosiderine, J. Biol. Chem. **82**:595, 1929.

concentrations of urobilin, urobilinogen [21] and coproporphyrin [22] in the urine and in the stools have been described elsewhere.

1. BLOOD PICTURE

The peripheral blood of 5 adult patients with paroxysmal nocturnal hemoglobinuria was characteristic of severe or of moderately severe chronic hemolytic anemia, as was evident from signs both of increased destruction of red blood cells and of active regeneration of blood. The major sign of destruction of blood and a fundamental feature of the disease was the finding of free hemoglobin in the blood plasma of all 5 patients at all times, whether hemoglobin was excreted in the urine or not. Apparently the hemoglobinemia is permanent, as has been stated by Hamburger and Bernstein.[4] The concentration of hemoglobin in the plasma varied from 11 to 280 mg. per hundred cubic centimeters; for the lower concentrations the presence of hemoglobin was not apparent on inspection of the samples but was measurable by the benzidine method and detectable by spectrophotometric examination. In urine free from red cells, oxyhemoglobin was identified by spectrophotometric methods. Quantitatively the amount of hemoglobin excreted in the urine in a twelve hour period varied over an extremely wide range (table 1). Although there was a direct relation between the level of plasma hemoglobin and the amount of hemoglobin appearing in the urine, there was no definite threshold for excretion of this protein. This corresponds with the observations of Ottenberg and Fox [23] for normal subjects receiving intravenous injections of hemoglobin solutions. Hemoglobin was usually absent from the urine when the hemoglobin content of the plasma varied from 15 to 30 mg. per hundred cubic centimeters. When the concentration in the plasma was 30 to 100 mg. per hundred cubic centimeters the urine usually showed significant amounts of hemoglobin, and when it varied from 100 to 250 mg. per hundred cubic centimeters the excretion frequently was extreme, the color of the urine varying from red to black. There were important exceptions to these generalizations, however; in case 4 hemoglobin was always present in the urine in detectable amounts when the level in the plasma was less than 30 mg. per hundred cubic centimeters; in case 1, on the contrary, no hemoglobin appeared in the urine for several days at a

21. Watson, C. J.: Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458, 1936.

22. Brugsch, J. T., and Keys, A.: Quantitative Separation and Estimation of Various Porphyrins in Biological Materials, Proc. Soc. Exper. Biol. & Med. **38**:557, 1938.

23. Ottenberg, R., and Fox, C. L.: The Rate of Removal of Hemoglobin from the Circulation and Its Renal Threshold in Human Beings, Am. J. Physiol. **123**: 516, 1938.

time with concentration in the plasma of from 60 to 120 mg. per hundred cubic centimeters. Undoubtedly the chronic hemosiderinuria observed in these cases and emphasized by others [24] is a direct result of the chronic hemoglobinemia. Although bilirubinemia was present, the degree of jaundice was less than might have been expected from the chronic hemoglobinemia. Similarly, the products of breakdown of hemoglobin were not excreted in amounts comparable to the amount of available free hemoglobin. The concentration of urobilinogen and of porphyrins in the urine and in the stools was normal or only moderately elevated. Decreased renal function was observed in the 3 cases in which examination was made and uremia occurred in case 3.

The accelerated production of red blood cells was evidenced by chronic reticulocytosis, the average percentage of reticulocytes in each of the 5 cases being between 10 and 28. The red blood cells varied from a normal to a moderately macrocytic mean corpuscular volume, as is found in other hemolytic anemias. In 3 patients (cases 1, 2 and 3) whose spleens had not been removed there were moderate leukopenia and thrombocytopenia, as observed by others.[25] Moderate splenomegaly was present in 2 of these patients (cases 2 and 3). In 2 patients, (cases 4 and 5) whose spleens had been removed several years prior to these observations the leukocyte counts and the platelet levels were normal. For all 5 patients the osmotic fragility of the red blood cells to hypotonic saline solutions was normal whether samples of blood were obtained during a severe or a mild hemolytic phase. Serologic tests for syphilis gave negative results, and the Donath-Landsteiner reaction was negative in the 4 cases in which the test was made. A summary of the blood chemistry and other laboratory observations is presented in table 1, and a brief review of each case is given in the appendix.

2. RELATION OF HEMOGLOBINEMIA TO SLEEP

Quantitative estimations of the concentration of hemoglobin in the plasma and urine were made for periods varying from three to six days on specimens obtained every three hours day and night or on specimens obtained at longer intervals. In cases 1 and 2, in which the spleens had not been removed, an increase in hemoglobinemia was always observed during sleep as compared to the level during waking hours; nocturnal hemoglobinuria was frequently present. A typical example of urinary excretion of hemoglobin during a hemolytic phase of moderate severity (case 1) is illustrated in chart 1. Since hemoglobinuria was an inconstant finding and did not necessarily indicate the variations in hemoglobinemia, the level of the plasma hemoglobin was studied quantitatively as related to sleep.

24. Marchiafava.[1] Micheli.[2] Witts.[3] Hamburger and Bernstein.[4]
25. Witts.[3] Hamburger and Bernstein.[4]

TABLE 1.—*Summary of Laboratory Observations on Five Patients with Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria*

Case Number	1	2	3	4	5
Sex	M	F	M	M	F
Age	17	39	48	35	30
Duration of disease (estimated to December 1938), years	3	4½	5½‡	6½	7
Period of observation	5 months	6 days	15 months	2 months	2 days*
Splenectomy	0	0	0	1935	1937
1. Plasma hemoglobin, mg. per 100 cc.					
Average	78	37	36	72	104
Range	29-252	36-83	Trace-195	23-279	
Number of determinations	136	13	167	78	1
2. Total excretion of hemoglobin in urine, mg.					
Awake, 12 hours					
Average	30†	0	310	850	After sleep:
Range	0-208		0-3300	30-2,600	2 specimens
Asleep, 12 hours					dark red;
Average	650	140	520	840	4+ benzidine
Range	160-1700	0-380	0-3100	30-3000	reaction
Number of determinations	9	4	206	60	
3. Red blood cells and hemoglobin					
Red blood cells, millions per cu. mm.					
Average	1.90	1.80	2.50	2.70	2.50
Range	1.50-2.60	1.70-1.90	1.44-3.50	1.70-3.00	1.90-3.80
Number of determinations	50	2	121	21	11
Hemoglobin, percentage					
Average	42	44	45	53	49
Range	27-55	42-46	20-60	38-71	40-74
Number of determinations	50	2	121	21	10
Reticulocytes, percentage					
Average	28	11	10	10	14
Range	13-47	6-17	0.2-28	0.2-24	3-20
Number of determinations	116	6	207	60	5
Hematocrit, percentage (average)	23	24	23	26	22
Mean corpuscular volume, cubic microns (average)	119	131	89	97	118
Mean corpuscular hemoglobin concentration (average)	29	29	30	31	29
Mean corpuscular diameter, microns	8.2	8.5	7.8	8.7	8.7
Standard deviation from mean diameter, microns	0.92	0.76	0.71	0.95	0.81
Coefficient of variation of diameters, percentage	11.2	8.9	9.0	11.0	9.2

4. White blood cells, thousands per cu. mm.					
Average	6.00	4.30	3.33	10.11‡	6.48‡
Range	1.4-7.4	4.1-4.5	1.3-6.8	5.7-14.8	4.9-7.2
Number of determinations	48	2	122	21	10
5. Platelets per cu. mm.					
Average	95,000	181,000	119,000	364,000‡	221,800‡§
Number of determinations	17	1	4	5	2
6. Bleeding time, minutes	1.5	2	3	1	..
7. Clotting time, minutes	12	7	9.5	9	..
8. Resistance of red blood cells to hypotonic salt solutions					
Trace of hemolysis, per cent salt	0.46	0.48	0.42	0.46	0.48
Definite hemolysis	0.44	0.46	0.40	0.42	
Button of cells unhemolyzed	0.30	0.36	0.30	0.24	
Complete hemolysis	0.26	0.28	0.26	0.22	0.35
9. Hemolysis test with acidified serum **	Positive	Positive	Positive	Positive	Positive
10. Donath-Landsteiner reaction **	Negative	Negative	Negative	Negative	....
11. Serologic test for syphilis	Negative	Negative	Negative	Negative	Negative
12. Serum bilirubin, mg. per 100 cc., range	0.5-1.8	0.8	0.11-1.33	0.3	0.2-3.6
13. Serum cholesterol, mg. per 100 cc., range	117	...	119-148	176	195
14. Plasma proteins					
Total protein, Gm. per cent	6.8	7.4	6.4	6.3	6.3
Albumin, Gm. per cent	4.6	4.5	4.6	4.1	
Globulin, Gm. per cent	1.9	2.7	1.6	2.2	
Fibrinogen, mg. per 100 cc.	310	250	180	350	
15. Nonprotein nitrogen, mg. per 100 cc., range	24-40	30	38-230	51-72	30
16. Blood group	Iv-0	IV-0	I-AB	IV-0	I-AB
17. Urea clearance, percentage of normal; average of 2 determinations	60	..	35 (December, 1938)	24	..

Patient died July, 1939; see case report and autopsy.
* Data supplemented by other observations; see case summary.
† See figure 1.
‡ After splenectomy.
§ 97,000 platelets before splenectomy.
** See tables 8, 9 and 10.

It was observed that increased hemoglobinemia was associated with sleep either at night or during the day (chart 2). The increase in hemoglobinemia did not occur if the patient was kept awake for twenty-seven hours, but it was noted when the patient slept during the day.

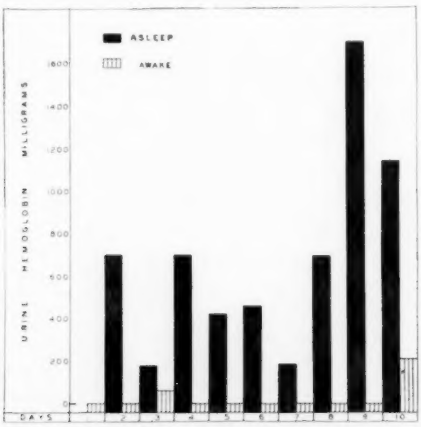

Chart 1 (case 1).—Relation of hemoglobinuria to sleep. Excretion of hemoglobin in the urine of a patient with paroxysmal nocturnal hemoglobinuria. The daily output was divided into two periods of twelve hours, a period of sleep (from 9 p. m. through 9 a. m.) and a period of waking (from 9 a. m. through 9 p. m.). The patient slept from 9 p. m. through 6 a. m.

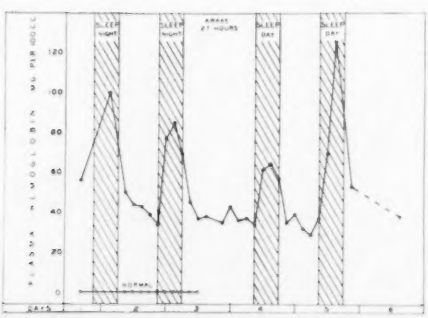

Chart 2 (case 1).—Chart showing that increased hemoglobinemia is related to sleep. The rise in hemoglobin content of the plasma was absent during twenty-seven hours without sleep and was reversed by sleep during the day.

To control the effect of posture and of ingestion of nourishment, the patient, case 1, was fed identical samples of food and fluids every three hours for forty-five hours (chart 3). For twelve hours he was kept awake at complete rest in bed in the positions assumed during sleep;

in the subsequent nine hours he was permitted to sleep except during feedings and venipunctures. It was evident that the increase in hemoglobinemia was correlated with sleep and not with posture, with ingestion of food or fluid, or with the time of day or night during which sleep occurred. However, in case 4, in which the spleen had been removed, there was no increase in hemoglobinemia or hemoglobinuria during sleep, although before splenectomy definite nocturnal hemoglobinuria had been observed by Hamburger and Bernstein.[4] The excretion of hemoglobin in the urine in case 4 for an eleven day period during a moderately severe hemolytic phase is illustrated in chart 4. In case 5, in which splenectomy also had been done, there was no opportunity to study the excretion of hemoglobin as related to sleep.

3. RELATION OF HEMOLYSIS IN VIVO TO ACID-BASE EQUILIBRIUM

Sleep is known to be associated with decreased pulmonary ventilation, with slight elevation of the carbon dioxide content of the arterial blood

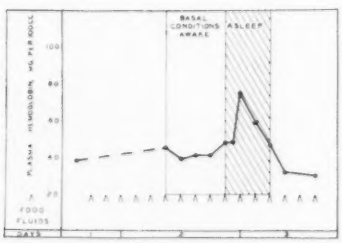

Chart 3 (case 1).—Chart showing that increased hemoglobinemia is related to sleep and not to posture or to ingestion of food and fluids. The patient received the same amount of food and fluids every three hours for forty-five hours. For twelve hours he was kept awake at complete rest in bed in the positions assumed during sleep. For nine hours he was allowed to sleep.

and with a consequent decrease in p_H, as observed by Hastings [26] and by Kleitman.[27] For this reason it was suspected that elevation of the hemoglobin content of the plasma during sleep was associated with variation in the acid-base equilibrium of the blood. To investigate this possibility, 2 patients were treated with acid and with basic salts; 1 was subjected to hyperventilation during sleep, and the p_H of the arterial blood and the carbon dioxide tension of a third patient were observed during sleep and during waking hours. Because of anemia none of the 5 patients was subjected to severe muscular exercise as a method of producing increased acidity of the blood.

26. Hastings, A. B.: Personal communication to the author.
27. Kleitman, N.: Sleep, Physiol. Rev. **9**:624, 1929.

The oral administration of ammonium chloride in case 1 (10 Gm. daily for two days followed by 5 Gm. daily for six days) was associated with an increase in hemoglobinuria during sleep for the first two days of treatment. For the subsequent six days of acid therapy and for a sixteen day period in which no acid treatment was given the urine contained only a trace of hemoglobin on three occasions. In case 4 the oral administration on two separate occasions of 5.7 Gm. and 12.7 Gm. respectively of ammonium chloride during twenty-four hours was accompanied by increase of hemoglobin in the plasma and in the urine and by decrease in the p_H of the arterial blood in the second instance from 7.33 to 7.23. In case 3, in which the patient had pyelonephritis, the administration of 4 Gm. of ammonium chloride and 12 Gm. of ammonium mandelate daily for six days did not produce an increase in hemoglobinemia or hemoglobinuria.

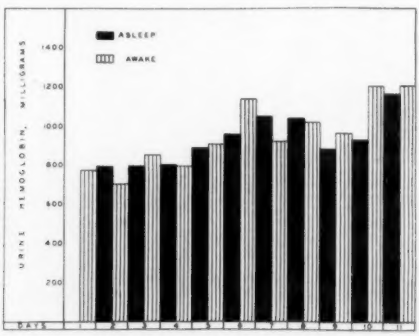

Chart 4 (case 4).—The chart shows the excretion of hemoglobin in the urine after splenectomy. No increase in hemoglobinuria was associated with sleep.

Sodium bicarbonate administered orally in the large dose of 65 Gm. in twenty-four hours produced a transient decrease in the hemoglobin content of the plasma and of the urine in cases 1 and 4. As is shown in chart 5, there was no significant rise in the value for plasma hemoglobin during sleep for the first night after ingestion of alkali; the carbon dioxide–combining power increased significantly with this therapy. For sixteen days the patient in case 1 received daily large doses of alkaline salts (40 Gm. of sodium bicarbonate for thirteen days and 56 Gm. of sodium citrate for three days). There was no excretion of hemoglobin for eight days, but in the subsequent period the nocturnal hemoglobinuria returned and increased materially, being associated with increase in the level of hemoglobin in the plasma. Administration of 45 Gm. of sodium bicarbonate during the sleeping hours without alkali during the day

produced a decrease in nocturnal hemoglobinuria but a large excretion of hemoglobin during waking hours. Complete and sudden withdrawal of alkali therapy, in contrast to discontinuing acid salts, produced extreme hemoglobinemia and hemoglobinuria in cases 1 and 4. In case 1 the concentrations of hemoglobin in the plasma reached levels of from 230 to 280 mg. per hundred cubic centimeters and the urine was red to black day and night. It was necessary to administer decreasing amounts of alkali over a period of six weeks to reduce in part the hemolytic activity. Because of the untoward effect of both the acid and the alkali salts in the amounts given, they were considered unsatisfactory for therapeutic administration.

The respiratory rate and depth during sleep were controlled artificially in case 1 by a Drinker respirator. During the first observations the rate of respiration and the volume of air exchange were adjusted to coincide with the spontaneous respiration of the patient. The usual rise in hemoglobin content of the plasma and of the urine was observed during natural sleep in the machine, and there was no significant alteration of alkali reserve as measured on samples of venous blood taken before and during sleep. Hyperventilation during a subsequent night was produced during six hours of natural sleep by increasing significantly the rate of respiration and the volume of air exchange. As is evident from the data in table 2, this hyperventilation produced significant alkalosis and was accompanied by no increase in hemoglobinemia or hemoglobinuria. However, during the same twenty-four hour period, natural sleep, without hyperventilation was associated with a more acid but normal p_H of the arterial blood and with a significant increase in hemoglobinemia and hemoglobinuria.

No significant alteration of p_H was demonstrable on samples of arterial blood obtained from the patient in case 2 during waking and sleeping hours (table 3). However, an increase of hemoglobin in both plasma and urine was associated with sleep.

4. RELATION OF HEMOLYSIS IN VITRO TO ACID-BASE EQUILIBRIUM

It was noted that on standing for four hours at room temperature or in the incubator at 37.5 C. samples of whole clotted blood (case 1), samples of defibrinated blood and samples of whole blood containing heparin as an anticoagulant all showed progressive hemolysis, with approximately 2 per cent destruction of red blood cells in the four hours. Comparable samples of blood from normal subjects showed no hemolysis. At ice box temperature there was minimal hemolysis of samples of the patient's blood. From these observations a change in p_H was suspected to be related to the increased hemolysis of samples standing at room temperature or incubator temperature. Accordingly,

TABLE 2.—*Effect of Alkalosis* on Hemoglobinemia*

Condition	Plasma Hemoglobin, Mg./100 Cc.	Urine Hemoglobin	Alkali Reserve (Total CO_2 at p CO_2 of 40 mm. mercury) Vol. per Cent	Arterial CO_2 Content, Vol. per Cent	Arterial Partial Pressure CO_2 Mm. of Mercury	p_H	Oxygen Capacity, Vol. per Cent	Oxygen Saturation, Percentage	Type of Blood
Awake and ambulatory	95-150	++ to +++	46.8				7.45		Venous
Natural sleep; respiration normal	230	++++	43.5	44.4	42.0	7.3	8.65	93.9	Arterial
Natural sleep; hyperventilation	140-150	+++	47.2	42.6	**28.0**	**7.47**	8.31	97.95	Arterial

* Alkalosis was produced during natural sleep by hyperventilation.

the influence of variation in p_H on hemolysis of samples of blood from each of the 5 patients was investigated with a variety of acids.

(*a*) *Carbon Dioxide.*—Equilibration of defibrinated blood from the patient or of his whole blood containing heparin with mixtures of oxygen and carbon dioxide produced hemolysis roughly proportional to the

TABLE 3 (Case 2).—*Plasma Hemoglobin and p_H of the Blood During Sleep* *

Status of Patient	Plasma Hemoglobin, Mg./100 Cc.	Arterial CO_2 Content, Vol. per Cent	Arterial Partial Pressure CO_2, Mm. of Mercury	p_H	Oxygen Capacity, Vol. per Cent	Oxygen Saturation, Percentage
Awake and ambulatory... (noon)	40	52.3	44.9	7.35	10.46	88.6
Asleep ..... (midnight)	85	50.4	43.9	7.35	9.49	98
Awake and ambulatory... (9 a.m.)	60	50.7	41.4	7.38	10.61	91

* Samples of arterial blood were taken during periods of both sleep and waking. Note that there was an increase of the hemoglobin content of the plasma during sleep but no significant change in p_H.

TABLE 4.—*Influence of Carbon Dioxide on the Degree of Hemolysis*

A. Samples of blood from the patient in case 1 and from a normal subject. Whole blood containing heparin as anticoagulant was equilibrated for 10 minutes at room temperature with the continuous flow of 2 liter samples of each gas mixture.

Gas Mixture, Percentage	Hemolysis of Patient's Blood, Percentage	Hemolysis of Normal Blood, Percentage	Gas Mixture, Percentage	Hemolysis of Patient's Blood, Percentage	Hemolysis of Normal Blood, Percentage
Air, 100	0	0	CO_2, 5 O_2, 95	4	0
CO_2, 2.5 O_2, 97.5	1	0	CO_2, 10 O_2, 90	4	0

B. Samples of blood from the patient in case 3 and from a normal subject. Whole defibrinated blood was washed with 2 liter samples of each gas mixture at room temperature for 20 minutes and equilibrated for an additional 10 minutes.

Gas Mixture, Percentage	Hemolysis of Patient's Blood, Percentage	Hemolysis of Normal Blood, Percentage	Gas Mixture, Percentage	Hemolysis of Patient's Blood, Percentage	Hemolysis of Normal Blood, Percentage
O_2, 100	0	0	CO_2, 10 O_2, 90	7	0
N_2, 100	0	0	CO_2, 10 N_2, 90	7	0

carbon dioxide tension when the partial pressure of carbon dioxide ranged from 4 to 40 mm. of mercury. This effect was related to the presence of carbon dioxide and not to the degree of oxygen saturation, since equilibration with oxygen, air or nitrogen alone caused no hemolysis and since the substitution of nitrogen for oxygen in the carbon dioxide mixtures caused no significant change in the degree of hemolysis (table 4). There was no hemolysis of normal red blood cells by the

aforementioned procedures when suspended in normal serum or in serum from the patient.

(*b*) *Lactic Acid and Sodium Bicarbonate.*—The addition to serum or to plasma (heparin) of lactic acid in a 10 or 20 millimolar concentration caused partial hemolysis of a 20 per cent suspension of washed red blood cells from the patient in fifteen minutes at room temperature. Hemolysis was further increased by subsequent equilibration of the suspension with carbon dioxide. The addition of sodium bicarbonate in a 10 or 20 millimolar concentration caused striking decrease in the hemolytic action of carbon dioxide. The addition of sodium chloride in the same concentrations did not inhibit hemolysis. The data from one experiment are shown in table 5. Therefore, the degree of hemolysis was apparently related to change in p_H. There was no hemolysis of

TABLE 5.—*Influence on Hemolysis by Carbon Dioxide of Lactic Acid and of Sodium Bicarbonate Added to Serum* *

	Hemolysis of Patient's Blood		Hemolysis of Normal Blood	
	Standing 30 Minutes at Room Temperature (No CO_2) Percentage	Equilibrated with 10 per Cent CO_2 and 90 per Cent O_2 for 10 Minutes at Room Temperature Percentage	Standing 30 Minutes at Room Temperature (No CO_2) Percentage	Equilibrated with 10 per Cent CO_2 and 90 per Cent O_2 for 10 Minutes at Room Temperature Percentage
Lactic acid	3	9	±	±
Unaltered serum	±	4	±	±
Sodium bicarbonate...	0	0.6	±	±

* The samples of blood were taken from the patient in case 2 and from a normal subject; washed packed red blood cells were used in 20 per cent suspension. Acid or alkaline solution was added to serum in a final concentration of 20 millimols and 5 per cent dilution of serum.

normal red blood cells in similar mixtures containing normal serum or serum from the patient.

(*c*) *Influence of p_H on Hemolysis.*—Further observations of the influence on hemolysis of the hydrogen ion concentration were made on samples of blood in cases 3 and 5, a variety of acids being employed and the effect being investigated of acidified serum from the patients and from normal subjects with blood of the same group on the washed red blood cells both of the patients and of normal subjects. For each acid a series of solutions containing a constant concentration of acid and varying amounts of sodium hydroxide was made, so that the addition of 5 per cent (by volume) of the mixture to serum produced a range of p_H of approximately 6 to 8. The first solution of each series contained no alkali. The only two variables, therefore, were the p_H and the salt concentration. The hydrogen ion concentrations of the mixture of serum and acid-alkali were estimated with rough accuracy

by the quinhydrone method.[28] The results of typical experiments are shown in chart 6 and table 6.

When the washed red blood cells from the patient in case 3 were suspended in serum from the patient or from normal subjects, hemolysis increased with increasing acidity for lactic, hydrochloric, nitric, acetic and sulfuric acids. Hemolysis was absent with citric acid and was

TABLE 6.—*Influence on Hemolysis of Certain Acids and Acid–Sodium Hydroxide Mixtures Added to Serum* *

Composition of Acid-NaOH Mixtures (Diluted to 100 Cc.) Acid†	4.5 N NaOH Volume Added Cc.	*p*H Resulting from Adding 0.05 Cc. of Acid-NaOH Mixture to 0.95 Cc. Serum	Hemolysis of Red Blood Cells (Case 3) Percentage	Hemolysis of Red Blood Cells from (Normal Subject) Percentage
A. Serum from Patient in Case 3.				
Control (unaltered serum)...		7.7	1	0
50 cc.	0	6.0	11	0
0.54 normal nitric acid	2	6.2	15	0
	8	7.6	0	0
	10	8.0	0	0
50 cc.	0	6.3	15	0
0.48 normal acetic acid	2	6.7	9	0
	8	7.8	0	0
	10	7.9	0	0
50 cc.	0	6.2	5	0
0.48 normal oxalic acid	2	6.5	3	0
	8	7.6	0	0
	10	8.0	0	0
50 cc.	0	6.2	3	0
0.40 normal orthophosphoric acid	2	6.6	3	0
	8	7.3	0	0
	10	7.6	0	0
B. Serum from Normal Subject				
Control (unaltered serum)...		7.7	0	0
50 cc.	0	6.5?	8	0
0.90 normal hydrochloric acid	2	6.8	7	0
	8	7.8	0	0
	10	8.2	0	0
50 cc.	0	6.5	7	0
0.50 normal sulfuric acid	2	6.8	1	0
	8	7.8	0	0
	10	8.2	0	0

* A 5 per cent suspension in serum of washed packed red blood cells from the patient in case 3 and from a normal subject of the same blood group were incubated for one hour at 37.5 C.

† Normality titrated with tenth-normal sodium hydroxide with the use of Tashiro's indicator.

diminished with oxalic and phosphoric acids in the concentrations employed. The degree of hemolysis varied somewhat with the serum used, whether from the patient or from a normal subject. No significant hemolysis occurred, however, when normal red blood cells were suspended in the acidified serums. The apparent inhibitory effect on hemolysis of citric acid of certain salts will be discussed later (section 8 *d*)

28. Hawk, P. B., and Bergheim, O.: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1937.

and in a second communication [9a] dealing with the complement activity of serum. It should be emphasized that hemolysis of the erythrocytes was frequently observed without the addition of acid and that hemolysis was always present and materially increased by the addition of certain acids and was decreased or eliminated by the addition of alkali. However, hemolysis was not caused by the effect of acid alone, as will be shown.

5. FUNDAMENTAL ABNORMALITY OF RED BLOOD CELLS

Although the p_H of plasma or serum influences the degree of hemolysis, a more important observation is the demonstration that the fundamental abnormality for this disease resides in the red blood cells and not in the serum. It has been shown that the washed red blood cells from these 5 patients were always hemolyzed in the acidified plasma

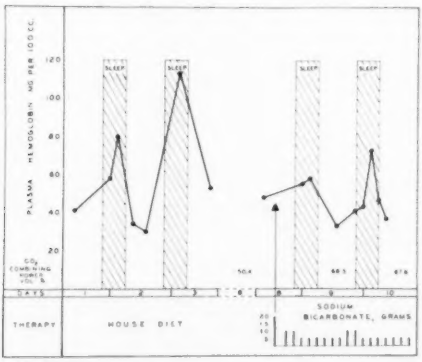

Chart 5 (case 1).—Influence of ingestion of alkaline salt on hemoglobinemia. The chart shows the concentrations of plasma hemoglobin during a period without therapy and after oral administration of large doses of sodium bicarbonate.

(heparin) or serum of the same blood group of all normal subjects tested. On the other hand, the washed red blood cells from normal subjects were never hemolyzed by the acidified plasma or serum of the 5 patients tested. Since the blood of the patients in cases 1, 2 and 4 was of group IV-O, it was possible to test their red cells with the serum of normal subjects with blood of all four groups. Since the blood of the patients in cases 3 and 5 was of group I-AB, it was possible to demonstrate the lack of hemolytic activity of their serums for the red cells from blood of all four groups from normal subjects. The erythrocytes and serums of 30 normal persons were employed in these observations. Accordingly, there was no apparent association of the four blood groups in this hemolytic system. The M and N blood groups were not tested.

(*a*) *Difference in Susceptibility of Red Blood Cells to Hemolysis.*—A difference in susceptibility of washed erythrocytes to hemolysis was demonstrated in cases 1 and 4 as well as in cases 3 and 5. Since the blood groups were the same for each pair of these 4 cases, it was possible to suspend washed erythrocytes from 2 patients in samples of the same serum and compare the degree of hemolysis. The data for one observation are shown in table 7. In both instances the erythrocytes showing the greater susceptibility to hemolysis were obtained from the patients in cases 1 and 5, who were in a moderately severe hemolytic phase, as evidenced by high concentrations of hemoglobinemia and hemoglobinuria. The other 2 patients, on the contrary, showed hemoglobinemia and hemoglobinuria which was moderate (case 3) or slight (case 4). There was definite evidence, therefore, first, of a difference

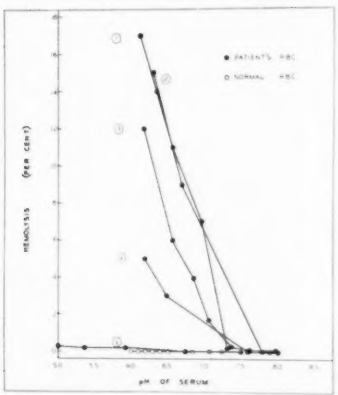

Chart 6 (case 3).—Influence on hemolysis of certain acids. The chart indicates hemolysis of erythrocytes from the patient in case 3 compared with the lack of hemolysis of normal erythrocytes, when suspended in serum from the same patient, acidified by the addition of a constant concentration of any one of the following acids, mixed with varying amounts of sodium hydroxide: (1) hydrochloric, (2) acetic, (3) lactic, (4) oxalic and (5) citric. The concentration of acid in serum for lactic and citric acids was 35 and 18 millimols, respectively. (For other acids see table 6.)

in susceptibility to hemolysis for erythrocytes from different patients and, second, of a correlation between hemolytic susceptibility of the erythrocytes *in vitro* and the clinical severity of the hemolytic process.

(*b*) *Effect of Erythrocyte Concentration on Hemolysis.*—The percentage of hemolysis of washed red blood cells varied inversely as the concentration of cells, as is evident from the curves in chart 7. Complete hemolysis was never observed under the conditions employed in this study. The usual range was from 2 to 30 per cent.

(*c*) *Effect of One Hemolytic Reaction on Susceptibility of Erythrocytes to Further Hemolysis.*—Washed red blood cells from the patient in case 1 were equilibrated with 10 per cent carbon dioxide and 90 per cent oxygen. After the first equilibration the cells were washed three times in saline solution and suspended at the same concentration in fresh serum for a second equilibration. The percentage of hemolysis was approximately the same for both equilibrations. There was no significant difference in the percentage of hemolysis between erythrocytes washed three times and those washed six times in saline solution. It was apparent, therefore, that the hemolytic susceptibility was not altered by multiple washings of the erythrocytes and also that erythrocytes susceptible to hemolysis still remained after one hemolytic reaction had occurred.

TABLE 7.—*Difference in Susceptibility to Hemolysis of Erythrocytes from Patients in Cases 3 and 5* *

Source of Red Blood Cells	Source of Serum	Hemolysis After Incubation for One Hour at 37.5 C	
		Without Acid, Percentage	0.05 Cc. 1/3 Normal HCl Added to 0.95 Cc. Serum, Percentage
Normal subject	Normal subject	0	0
	Patient (case 3)	0	0
Patient (case 3)	Normal subject	0	10
	Patient (case 3)	0	13
Patient (case 5)	Normal subject	5	15
	Patient (case 3)	8	16

* A 5 per cent suspension of washed packed red blood cells was used. All samples were of blood group I-AB.

6. FRESH HUMAN PLASMA OR SERUM REQUIRED FOR HEMOLYSIS

Hemolysis of the abnormal erythrocytes in all 5 cases occurred only in fresh human plasma (heparin) or serum. Hemolysis did not occur in physiologic solution of sodium chloride or in plasma or serum which had been heated for thirty minutes at 50 or at 56 C. Therefore, a factor present in human plasma (heparin) and serum was essential for hemolysis of the abnormal red blood cells. The relation of this factor to the complement activity of human serum will be discussed in detail in another communication.[9a]

(*a*) *Effect of Exposing Serum to Various Temperatures for Thirty Minutes.*—Serums exposed to a temperature of 50 or 56 C. for thirty minutes showed no hemolytic activity for the washed red blood cells of any of the 5 patients. There was no striking difference in the activity of serums exposed for thirty minutes at temperatures of from 0 to 40 C.

(*b*) *Effect of Dilution of Serum.*—The hemolytic activity of serums was decreased by dilution with saline solution or with serum heated at 56 C. for thirty minutes. Hemolysis was seldom demonstrable in dilution beyond 1 to 3 or 1 to 4. In some instances the hemolytic activity of serum was not demonstrable in a 1 to 2 dilution.

(*c*) *Failure of Guinea Pig Complement to Reactivate Heated Serum.*—The hemolytic activity was not restored to serum heated at 56 C. for thirty minutes by the addition of sufficient guinea pig serum to reestablish or increase the original complement concentration of the serum as measured by sensitized red blood cells. This will be discussed in another communication.[9a]

(*d*) *Inhibition of Hemolysis by Certain Salts.*—The hemolytic activity of carbon dioxide was prevented by the addition to whole blood,

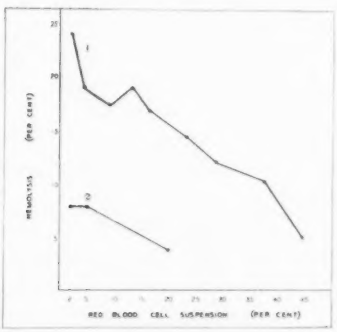

Chart 7 (case 3).—Effect of erythrocyte concentration on hemolysis. Curve 1 indicates washed packed red blood cells from the patient suspended at varying concentrations in samples of a pooled specimen of serum from the same patient containing lactic acid (20 millimols). The suspensions were incubated for two hours at 37.5 C. Curve 2 indicates washed packed red blood cells from the patient in case 1 in serum from the same patient. The suspensions were equilibrated at room temperature for ten minutes with 10 per cent carbon dioxide and 90 per cent oxygen.

to plasma (heparin) or to serum of sodium citrate (0.3 per cent), potassium oxalate (0.2 per cent) or potassium cyanide (0.13 per cent). One tenth of the aforementioned concentration of potassium cyanide (0.01 per cent), however, did not inhibit hemolysis. The hemolytic activity of serum treated with 0.13 per cent potassium cyanide or of serum heated at 56 C for thirty minutes was not restored by the addition of a 0.4 per cent solution of methylene blue in a concentration of 0.01 or 0.1 Gm. per hundred cubic centimeters. Susceptibility of the erythrocytes to hemolysis was not altered by exposure to these salts. Washed red blood cells obtained from samples of whole blood containing the aforemen-

tioned salts showed the same hemolytic reactions as did untreated cells when resuspended in fresh serum. The inhibitory effect of these salts, therefore, apparently was on the serum factor or on the interaction between the serum factor and the red blood cell.

7. DONATH-LANDSTEINER REACTION: CHILLING OF BODY

The manifestations of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria are contrasted (table 8) with the manifestations of paroxysmal hemoglobinuria from chilling. In the nocturnal type of disease the Donath-Landsteiner reaction is negative and chilling of the body does not produce a paroxysm of intravascular hemolysis. However, the observation that the patient's red blood cells are frequently hemolyzed to some extent in his own serum during incubation might falsely suggest a positive Donath-Landsteiner reaction. In contrast to the Donath-Landsteiner phenomenon, the patient's serum does not hemolyze normal cells, and previous chilling is not necessary for hemolysis. Further clarification may be made by the hemolysis test with acidified serum. A paroxysm of hemoglobinuria is not induced in the nocturnal type of disease by exposure to cold, yet the presence of variable degrees of hemoglobinemia or the frequent occurrence of hemoglobinuria has caused this disease to be mistaken for paroxysmal hemoglobinuria é frigore.

COMMENT

It is apparent that the fundamental abnormality underlying the hemolytic mechanism in the disease chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria resides in the red blood cells. A thermolabile factor essential for hemolysis was found in the patients' plasma and serum and also in the plasma and serum of normal subjects. The patients' serum, however, exhibited no hemolytic action on normal red blood cells. Increase of acidity of plasma or serum within or beyond the physiologic range always produced an increase in the degree of hemolysis; decrease of acidity diminished or eliminated hemolysis. Accordingly, this disease may be distinguished in vitro from other hemolytic anemias by a hemolysis test with acidified serum (tables 9 and 10). This test has shown no hemolysis with samples of blood from patients with hemolytic jaundice, hemolytic anemia with sulfanilamide poisoning, acute hemolytic anemia of Lederer, sickle cell anemia, Cooley's anemia, paroxysmal hemoglobinuria with chilling (carbon dioxide equilibration by van den Bergh [6] and Jordan [9]), pernicious anemia, hypochromic anemia and alcoholic cirrhosis of the liver with anemia.

Two simplified methods of performing the hemolysis test with acidified serum are as follows. Blood defibrinated with glass beads is

TABLE 8.—*Comparison of Certain Features of Paroxysmal Nocturnal Hemoglobinuria and Hemoglobinuria from Chilling*

Feature of Disease	Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria (Marchiafava-Michell Disease)	Paroxysmal Hemoglobinuria from Chilling (Donath-Landsteiner)
1. Fundamental abnormality	In the red blood cells	In the serum (hemolytic antibody)
2. Donath-Lansteiner reaction	Negative	Positive (hemolytic antibody fixed to red cells only in cold)
3. Hemolysis by patient's serum of normal red blood cells of same blood group	None	All red blood cells hemolyzed by antibody in Donath-Landsteiner reaction
4. Complement required for in vitro hemolysis	Fresh human serum, required for hemolysis, complement or complement-like substance;* not supplied by guinea pig serum	Complement required; supplied by human serum or by guinea pig serum
5. Hemolysis on incubation alone; serum and red blood cells at 37.5 C.	Patient's cells frequently hemolyzed by any serum; normal cells not hemolyzed by patient's serum	None
6. Hemolysis test with acidified serum; p_H adjusted to approximately 6.5 with lactic acid, hydrochloric acid or equilibration with CO_2-O_2 mixture; serum and red blood cells incubated at 37.5 C. for one hour	Patient's cells hemolyzed significantly by fresh human serum; normal cells not hemolyzed by patient's serum; same blood groups employed	No hemolysis of patient's cells in patient's serum exposed to CO_2 at 37 C. (Van den Bergh [6] and Jordan [9])
7. Hemoglobinemia	Chronic; usually increased during sleep	Absent except during reaction following chilling of the body
8. Hemoglobinuria	Frequent; usually greater during sleep (paroxysmal nocturnal hemoglobinuria)	Absent except during reaction following chilling of body (paroxysmal hemoglobinuria é frigore)
9. Chilling of body	Does not produce hemolytic episode	Produces paroxysm of intravascular hemolysis with hemoglobinemia and hemoglobinuria
10. Syphilis	Absent	Usually present
11. Anemia	Chronic hemolytic anemia	Acute anemia following paroxysm; no anemia between attacks

* To be discussed in another communication.[9a]

employed, since anticoagulants other than heparin inhibit the hemolysis completely. In the first method, 5 cc. of defibrinated whole blood is equilibrated in an ordinary tonometer for fifteen minutes at room temperature with a gas mixture containing 10 per cent carbon dioxide and 90 per cent oxygen (table 4). The suspension is then centrifuged. Blood from a patient with paroxysmal nocturnal hemoglobinuria shows from 5 to 30 per cent hemolysis after such equilibration, whereas blood from a normal subject should show no hemolysis or only a trace. In the second method, 10 cc. of defibrinated blood is centrifuged for removal of serum; the erythrocytes are made to a 5 per cent suspension in salt solution, and two samples of 1 cc. each are measured into small tubes and the salt removed after centrifugation. The packed erythrocytes of one tube are suspended in 1 cc. of unaltered serum; those of the other tube are suspended in a mixture containing 0.95 cc. of serum and 0.05 cc. of ⅓ normal hydrochloric acid (p_H, approximately 6.5); these are incubated for 1 hour at 37 C. and centrifuged. In paroxysmal nocturnal hemoglobinuria the tube containing unaltered serum may show no hemolysis or lysis of from 1 to 10 per cent; the tube containing acidified serum will show a greater degree of hemolysis, varying from 2 to 30 per cent. There should be no significant hemolysis in either tube for blood samples from normal subjects or from persons with other diseases. If the test gives a positive result, suitable controls may be set up as outlined in tables 7, 9 and 10.

Van den Bergh,[6] in 1911, reported observations in vitro similar in part to those just described in the case of a patient with hemolytic anemia associated with the crises of hemoglobinuria (undoubtedly the syndrome later identified by Marchiafava and Micheli). Van den Bergh found that the patient's red blood cells were hemolyzed at 37 C. in an atmosphere containing carbon dioxide when suspended in the serums from the patient and from 2 normal subjects; the blood groups were not mentioned. The patient's serum did not hemolyze normal cells. He also observed that heating serum for thirty minutes at 50 C. destroyed the hemolytic activity of the serum and that hemolysis was not restored by adding small amounts of fresh human or guinea pig serum. The author concluded that the hemolysis was caused not by specific hemolytic substances in the serum but by an abnormal "fragility" of the erythrocytes to carbon dioxide which did not manifest itself in contact with dilute solutions of sodium chloride. However, as was shown by van den Bergh in this case and by all subsequent investigators, the resistance of red blood cells to hypotonic salt solutions is normal. This disease, therefore, is unrelated to acquired or to congenital hemolytic jaundice characterized by abnormally increased osmotic fragility of the erythrocytes to hypotonic solutions.

TABLE 9.—*Donath-Landsteiner Reaction Compared to Result of Hemolysis Test with Acidified Serum*

Source of Serum	Treatment of Serum	Source of Red Blood Cells	Treatment of Suspension of Red Blood Cells (15%) in Serum	Color of Supernatant Serum	Hemoglobin Concentration of Supernatant Serum, Mg./100 Cc.	Hemolysis,† Percentage	Comment
Patient (case 3)	Unaltered	No Cells Added		Light brown	60		Hemoglobin present in serum before use
Control				Straw	15		
Patient (case 3)	Unaltered	Patient (case 3)	Chilled to 1 C. for 30 minutes; incubated at 37.5 C. for 2 hours	Pink	85	0.5*	Donath-Landsteiner reaction without added complement
		Control		Straw	70	0.2	
Patient (case 3)	Unaltered	Patient (case 3)	Incubated at 37.5 C. for 2 hours	Pink	100	0.8*	Incubation without chilling
		Control		Straw	60	0.2	
Patient (case 3)	Serum acidified with lactic acid (20 millimols)	Patient (case 3)	Incubated at 37.5 C. for 2 hours	Dark red	510	8	Hemolysis test with acidified serum
		Control		Straw	60	0.2	
Control		Patient (case 3)		Dark red	575	10	
		Control		Straw	20	±	

* Hemolysis has been observed as high as 10 per cent in other cases after incubation.

† Note that the patient's cells were the only red blood cells to be hemolyzed; chilling did not increase the hemolysis; a normal serum gave the same hemolytic reactions as the patient's serum; acidified serum produced significant hemolysis only of the patient's red blood cells.

The hemolytic system in nocturnal hemoglobinuria differs distinctly from that of paroxysmal hemoglobinuria from cold. In the latter disease the red blood cells are normal; the serum contains a true hemolytic antibody absorbed in the cold by erythrocytes, and after chilling hemolysis occurs in the presence of complement on incubation at 37 C. (Donath-Landsteiner reaction). The mechanism of hemolysis in hemoglobinuria from exertion (*Marschhemoglobinurie*) is not understood (Witts;[3] Hamburger[4]).

The in vivo observations in cases of paroxysmal nocturnal hemoglobinuria have demonstrated the presence of free hemoglobin in the plasma at all times, indicating continued intravascular hemolysis. The administration of acid-forming salts produced a significant increase in acidity of arterial blood and a transient increase in hemoglobinemia and hemoglobinuria in 2 cases in which there were no complications but failed to do so in 1 case in which acute pyelonephritis was an associated condition. Conversely, a decrease in acidity of the blood, produced by the administration of alkaline salts and by alkalosis from hyperventilation, was associated with transient decrease in intravascular hemolysis. These observations were made on 2 patients, 1 with the spleen intact and the other with spleen removed.

The nocturnal increase in hemoglobinemia was shown to be associated with sleep and not with the patient's posture, with ingestion of food and fluid or with the time of day or night during which sleep occurred. No rise in the hemoglobin content of the plasma occurred during twenty-seven waking hours. It is probable that the increased intravascular hemolysis which occurs during sleep is associated with the increase of acidity of peripheral blood, especially in certain regions of the body subject to relatively inactive circulation at this time.

In 1 case (case 4) typical nocturnal hemoglobinuria had been observed before splenectomy. After splenectomy the nocturnal element of the hemoglobinuria was eliminated without alteration of the fundamental abnormality of the red blood cells or significant decrease of the anemia. Destruction of red blood cells is thought to occur within the splenic pulp, where anatomic and physiologic observations[29] have demonstrated ample opportunity for stasis. It appears likely, therefore, that splenectomy in this case had removed an organ which previously had provided a region of stasis during sleep and apparently a region of acidity even greater than the acidity of the peripheral blood. Increased stasis during sleep, therefore, especially in the spleen, may provide in part the increased acidity responsible for the nocturnal element of hemoglobinemia and hemoglobinuria.

29. McNee, J. W.: Spleen: Its Structure, Functions and Diseases (Lettsomian Lecture), Lancet **1**:951, 1009 and 1063, 1931.

TABLE 10.—*Diagnostic in Vitro Tests for Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria*

Tube No.	Treatment of Serum (Fresh Serums from Patient or from Normal Subject† of Same Blood Group)	Hemolysis*		Comment
		Patient's Red Blood Cells (5 per cent suspension in serum) Percentage	Normal Red Blood Cells (5 per cent suspension in serum) Percentage	
1	Unaltered serum	0-10	0	Patient's cells may or may not be hemolyzed by unaltered serum containing no added acid
2	Acidified serum (0.95 cc. serum + 0.05 cc. 1/3 normal HCl)	2-30	0-±	Patient's cells always hemolyzed by acidified serum; no hemolysis of normal cells
3	Heat-inactivated acidified serum (0.95 cc. serum heated at 56 C. for 5 minutes + 0.05 cc. 1/3 normal HCl)	0	0	Heated serum (acidified) produces no hemolysis
4	Heat-inactivated serum (acidified) + guinea pig complement (0.75 cc. serum heated at 56 C. for 5 minutes + 0.05 cc. 1/3 normal HCl + 0.20 cc. undiluted guinea pig serum)	0	0	The addition of large amounts of guinea pig complement does not restore the hemolytic activity of heated serum [9a]

* Samples incubated for 1 hour at 37.5 C.

† Normal serum gave the same hemolytic reactions as did the patient's serum.

No satisfactory form of therapy was found for this disease. The use of alkaline salts was complicated by severe hemolytic episodes on their withdrawal or during their administration. Acid-forming salts increased hemolysis temporarily and are potentially dangerous in producing damage of the renal tubules by precipitation of hemoglobin.[30] Splenectomy in the 2 cases observed did not decrease the anemia. Antisyphilitic therapy administered to the patient in case 3 did not alter the course of the disease. Transfusions are usually associated with hemolytic reactions of varying severity but also are followed by periods ranging from several days to weeks during which the rate of intravascular hemolysis is strikingly decreased, as evidenced by low levels of hemoglobin in the plasma and in the urine and by increase of the red blood cell and hemoglobin content of the peripheral blood. In one instance (case 3) a transfusion reaction was followed by oliguria and uremia. Transfusions may be used guardedly as supportive measures. Conservative treatment consists of administration of iron by mouth, a good diet, moderate activity and avoidance of infections.

This disease has received many names, with resulting confusion in classification. As has been suggested by Hamburger and Bernstein, the term "chronic hemolytic anemia" certainly describes one essential feature of the syndrome. However striking may be the appearance of "paroxysmal nocturnal hemoglobinuria," it must be emphasized, first, that hemoglobinemia was present continuously in all cases and is a fundamental feature of this disease; second, that hemoglobinuria undoubtedly results from the excretion of the free hemoglobin circulating in the plasma; third, that hemoglobin may be absent from the urine for intervals varying from days to weeks, and fourth, that an increase in the hemoglobin content of the plasma during sleep ("nocturnal") was always observed in patients with intact spleens even when the urine was free from hemoglobin. Therefore, hemoglobinuria is not a true index of the concentration of hemoglobin in the plasma. For these reasons this disease might be described more accurately by the term chronic hemolytic anemia with paroxysmal nocturnal hemoglobinemia.

SUMMARY AND CONCLUSIONS

In chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli disease) the fundamental abnormality resides in the red blood cells.

30. DeGowin, E. L.; Warner, E. D., and Randall, W. L.: Renal Insufficiency from Blood Transfusion: II. Anatomic Changes in Man Compared with Those in Dogs with Experimental Hemoglobinuria, Arch. Int. Med. **61**:609 (April) 1938.

A thermolabile factor essential for hemolysis was found in the plasma and serum of 5 patients and of all normal subjects examined.

The patients' plasma and serum exhibited no hemolytic action on normal cells.

In vitro, the patient's washed red blood cells suspended in plasma or serum from the patient or from normal subjects were hemolyzed frequently but not always at a normal p_H; hemolysis was always produced by increasing the acidity of plasma or serum within or beyond the physiologic range of variation in p_H; hemolysis was diminished or eliminated by decreased acidity.

In vivo, free hemoglobin was present at all times in the plasma, indicating continued intravascular hemolysis. Increased acidity produced by ingestion of acid-forming salts was associated with a transient increase in hemoglobinemia and hemoglobinuria in 2 of 3 cases. Alkalosis produced by ingestion of alkaline salts and by hyperventilation was associated with a transient decrease in hemoglobinemia and hemoglobinuria.

Nocturnal hemoglobinemia was associated with sleep and not with the patient's posture, with ingestion of food or fluid or with the time of day or night during which sleep occurred. It is suggested that increased hemoglobinemia and hemoglobinuria during sleep are induced by increased intravascular hemolysis associated with increased acidity of blood, especially of regions of the body subject to stasis, such as the spleen.

Splenectomy in 2 cases did not alter the fundamental abnormality of the red blood cells or decrease significantly the anemia. In 1 patient studied before and after splenectomy removal of the spleen was associated with elimination of the rise in hemoglobinemia and hemoglobinuria during sleep.

Administration of alkaline salts was unsatisfactory as a therapeutic measure, withdrawal of the therapy producing severe and prolonged hemoglobinemia and hemoglobinuria.

The blood picture, laboratory findings and clinical records in 5 cases are reported. Four of the cases have not been previously reported.

It is suggested that this disease be called chronic hemolytic anemia with paroxysmal nocturnal hemoglobinemia.

APPENDIX: REPORT OF CASES

CASE 1.—A Canadian-born school boy aged 17 was admitted to the Boston City Hospital in March 1937.

History.—The patient was in good health until the age of 15, when, in 1935, he first noticed shortness of breath on exertion, increased fatigability and listlessness for several months preceding an attack of influenza which was followed by the development of pallor with moderate jaundice, symptoms which continued to

the time of examination. He was anemic, there being 2,620,000 red blood cells per cubic millimeter, with 50 per cent hemoglobin. This condition was first observed in March 1936, and has continued, with periods of increased severity, to the time of this report. The urine was first observed to be "the color of blood" after a second infectious episode, with fever, cough and prostration, in June. During this period the urine was dark red continuously for several days. There were no further observations on the color of the urine. For the subsequent eight months the patient was chronically ill with varying degrees of jaundice. The red blood cell count varied from 1,240,000 to 1,770,000 per cubic millimeter. During this interval one transfusion was given, without apparent reaction and with some benefit. In addition, large doses of liver extract by intramuscular injection were administered, together with large amounts of raw liver, desiccated hog stomach (ventriculin) and iron given by mouth. During the three months before admission the jaundice had decreased and the patient was ambulatory, with a good appetite and few complaints other than pallor and easy fatigability.

Past History.—At the age of 12 the patient had pneumonia on the left side, with pleurisy but without known sequelae. In 1935, after a body blow, he noted "smoky" urine for one day only.

Family History.—There was no familial history of anemia, jaundice or hemoglobinuria. The patient's mother had hay fever and diabetes mellitus, his maternal grandmother had had asthma. Four siblings were well.

Physical Examination.—The patient was athletic and well nourished. He was pale, with moderate icterus of the scleras and light yellowish brown tinting of the skin. There were papular eruptions of acne on the face and healed scars over the shoulders. The temperature and the pulse rate were normal. The blood pressure was 120 mm. of mercury systolic and 65 mm. diastolic. There was a systolic murmur over the apex of the heart.

Laboratory Observations.—As has been mentioned, large amounts of hemoglobin were excreted in the urine, especially after sleep, with or without hemoglobinuria during waking hours (chart 2). For periods of from three days to two weeks the urine was entirely free from hemoglobin. Hemoglobinemia was always present (charts 2 and 3). The laboratory observations concerning the blood are summarized in table 1. The specific gravity of the urine varied from 1.002 to 1.035. There was a trace of albumin in specimens containing no hemoglobin. The sediment of the urine showed no red blood cells, occasional casts, constantly present hemosiderin and moderately increased urobilinogen, but no bile. The stools contained no occult blood. The Takata-Ara reaction was negative. The van den Bergh reaction was indirect. The calcium content of the serum was 9.6 mg., the phosphorus content 5.5 mg. and the vitamin C content 0.5 mg. per hundred cubic centimeters; the basal metabolic rate was + 12 per cent. The gastric contents after injection of histamine yielded 57 units of free acid. Cutaneous tests showed no sensitivity to pollens, food or certain other test substances. Roentgen examination revealed no abnormalities of the skull or chest; the long bones were normal except for a posttraumatic osteoma of the right tibia. Culture of pus expressed from an acne lesion showed Staphylococcus aureus.

Progress.—After periods during which the urine was free of hemoglobin, nocturnal hemoglobinuria returned without apparent cause and without other symptoms or signs. Hemolytic episodes of varying severity were associated with (1) an infection of the upper respiratory tract, (2) oral administration of 10 Gm. of ammonium chloride daily for two days, (3) intravenous injection of 1 Gm. of unneutralized ascorbic acid, (4) a febrile reaction to the eighth consecutive daily

intramuscular injection of 5 cc. of liver extract (liver extract-Lilly N. N. R), (5) withdrawal of alkali therapy (40 Gm. sodium bicarbonate given by mouth daily) and (6) transfusion of 500 cc. of citrated blood. Severe hemolytic episodes were not necessarily associated with fever or chills but were always associated with some fatigue; there was no pain, dysuria or nausea. Transfusion was followed by a febrile reaction for twenty-four hours, with extreme hemoglobinemia and hemoglobinuria during the second and third days after transfusion. Hemoglobin disappeared from the urine on the third day, with a striking decrease in hemoglobinemia and hemoglobinuria. Hemoglobinuria was absent for two weeks, returning in slight amounts nocturnally in the subsequent two weeks. No apparent benefit was observed after the intramuscular injection of liver extract, the intravenous and intramuscular injection of 1 Gm. or 0.5 Gm. daily of ascorbic acid and the oral administration of iron and of liver extract (Valentine).

In the sixteen months since the patient's discharge from the hospital, in August 1937, he has returned to Canada and successfully continued his studies at boarding school. Except for acute attacks he has usually felt well, taking part in moderate exercise and enjoying normal activity with the limitation of somewhat increased fatigability. The disease has remained unchanged, however, the blood count varying from 1,510,000 to 2,410,000 red cells per cubic millimeter and the concentration of hemoglobin from 38 to 53 per cent. Five infections of the respiratory tract, including purulent otitis media, produced severe hemoglobinuria in 4 instances. Four transfusions were followed by from three to four days in which the urine was dark red and a subsequent period of from three days to three weeks without apparent hemoglobinuria. The only treatment other than transfusion has been administration of ferrous sulfate by mouth, 12 grains (0.78 Gm.) per day.

CASE 2.—A woman aged 39, a minister's wife living in New Hampshire, was admitted to the Boston City Hospital in October 1937.

History.—The patient felt well until the summer of 1934, when the insidious onset was noted of increased fatigability, palpitation and pallor. No jaundice was present. There were no other symptoms. Slight jaundice was observed in November 1934, together with anemia. The latter condition had been treated with large amounts of liver extract given parenterally and of liver extract and iron given by mouth, without apparent benefit.

In the subsequent three years preceding her admission to the hospital the patient showed chronic anemia and intermittent jaundice. The urine on occasions was red or black, especially after sleep; exacerbations appeared to follow infections of the respiratory tract and indigestion associated with ingestion of fat. During acute episodes the patient remained in bed because of fatigue and palpitation; at other times she was able to partake in moderate activity. The maximum red cell blood count observed in this period was 2,500,000 per cubic millimeter, and the maximum concentration of hemoglobin was 65 per cent. The resistance of the erythrocytes to hypotonic saline solutions was normal. Serologic tests for syphilis gave negative results. Analysis of the gastric contents after a test meal revealed free hydrochloric acid. Several therapeutic regimens were without striking benefit, namely, a Sippy diet with alkaline powders, large doses of iron by mouth and a second series of intramuscular injections of liver extract.

Past History.—Sore throat associated with moderate fever, lymphadenitis of the neck and prostration for from two to three days had occurred approximately once each winter for many years. Menstruation had been normal. There had been no pregnancies.

Family History.—There was no familial history of anemia, jaundice or hemoglobinuria. Two siblings had died at 25 and at 30 years of age respectively of pulmonary tuberculosis. A third had died at the age of 30 of heart disease. Four siblings were well.

Physical Examination.—The patient was slight in stature but was well developed and well nourished. She appeared to be in good health except for moderate pallor and a slight brownish yellow tint to the scleras. The temperature and pulse rate were normal; the blood pressure was 130 systolic and 60 diastolic. A rough systolic murmur was heard over the apex of the heart. The tip of the spleen was palpable.

Laboratory Observations.—The laboratory observations concerning the blood are summarized in table 1. The maximum specific gravity of routine specimens of urine was 1.023; a trace of albumin was found in specimens containing no hemoglobin; the sediment contained hemosiderin, occasional casts and white and red blood cells. The stools showed no occult blood. The Takata-Ara reaction was negative. The basal metabolic rate was + 6 per cent. Roentgen examination of the chest showed small areas of calcification at the apexes of both lungs, compatible with healed tuberculosis. Roentgen examination of the abdomen revealed moderate splenomegaly.

Progress.—During one week of observation the patient received no therapy other than the administration of iron by mouth. She had never received a transfusion.

In the year since her discharge from this hospital there have been no major hemolytic episodes, but the patient has noted bouts of nocturnal hemoglobinuria. She maintained moderate activity.

Case 3.—An Italian man aged 48, an unemployed contractor, was admitted to the Boston City Hospital in April 1938, which was fourteen months before his death in July 1939.

History.—This patient enjoyed good health until February 1934, when he complained of intermittent dull pain in the lumbar region, radiating to the abdomen and to the left testicle and associated with the passage of red urine.

In the subsequent four years he was admitted to another hospital on four occasions (in 1934, 1936 and 1937). Throughout this period there were intermittent attacks of hemoglobinuria associated with symptoms of fatigue, vague malaise, occasional dysuria and frequency of voiding, pallor and moderate jaundice. Physical examination revealed moderate splenomegaly.

Chronic anemia was present at all times, the number of red blood cells varying between 2,290,000 and 3,790,000 per cubic millimeter and the hemoglobin content between 40 and 70 per cent. The urine always showed white cells and frequently showed hemoglobin, but without red blood cells. The urine concentration test showed the maximum specific gravity to be 1.020. A maximum nonprotein nitrogen content of 80 mg. per hundred cubic centimeters was observed in 1934; the maximum value was 30 mg. in 1937. Determinations of phenolsulfonphthalein in the urine after intravenous injection of the dye showed diminished total excretion after sixty-five minutes, 13 per cent in 1934 and 25 per cent in 1937. Values for serum bilirubin of 2.5 mg. and 2.2 mg. were observed in 1936 and 1937 respectively. Cystoscopic and retrograde pyelographic examination showed no abnormality of the bladder, ureters or kidneys. Roentgen examination of the chest and gastrointestinal tract revealed no abnormality. One of four Hinton tests was reported as giving a slightly positive result. The patient received antisyphilitic therapy

without benefit to the anemia and with the development of severe jaundice and of stomatitis. A total of four doses of bismuth salicylate and nine doses of arsphenamine was administered. The Donath-Landsteiner reaction was negative, and chilling of the arm did not produce a hemolytic episode.

Past History.—The patient had lived in Italy until the age of 17. There was no history of malaria. Gonorrhea was contracted at the age of 20 and apparently again in 1935. Before the present illness, as much as a pint of whisky and a bottle of wine had been consumed daily for several years.

Family History.—There was no familial history of anemia, jaundice or hemoglobinuria. Seven siblings were well. Nine children of the patient were well.

Physical Examination.—The patient was well developed and well nourished and appeared in good health except for moderate pallor and slight icterus of the scleras. The pupil of the left eye was deformed owing to trauma. The temperature and the pulse rate were normal. The blood pressure was 150 systolic and 90 diastolic. The tip of the spleen was palpable.

Laboratory Observations.—The laboratory observations concerning the blood are summarized in table 1. The maximum specific gravity of routine specimens of urine was 1.020. A heavy trace of albumin was present in specimens containing no hemoglobin; the sediment showed hemosiderin, casts, white blood cells and rare red blood cells. The stools showed no occult blood. The Takata-Ara reaction was negative.

Progress.—During the fifteen months before death the patient was admitted to the Boston City Hospital on four occasions for a total period of one year. Throughout the patient's hospitalization the urine contained hemoglobin in varying amounts except on the following occasions: in five instances after transfusion of 500 cc. of citrated whole blood; in two instances after transfusion of washed red blood cells derived from 500 cc. of whole blood; on one of two occasions after intramuscular injection of washed stroma prepared from washed red blood cells, and for several periods of two to three weeks during the active stage of pyelonephritis, which was present for the five months preceding his death. In the aforementioned instances the hemoglobinemia decreased strikingly, and the hemoglobinuria disappeared entirely for two to four days, or for longer when associated with the renal infection. This was followed by the gradual return first of nocturnal hemoglobinuria and then of hemoglobinuria at all times, the greatest excretion occurring during sleep. A severe hemolytic episode occurred coincidentally with an infection of the upper respiratory tract. Moderately severe hemolytic episodes occurred associated with abscesses of two molar teeth and their removal, for from two to three days after transfusion of citrated whole blood or of washed red blood cells and after the intravenous injection in divided doses during two days of 80 cc. of a 50 per cent suspension of stroma from red blood cells in physiologic solution of sodium chloride. Clinically the patient was ambulatory, complaining only of moderate fatigue until the onset of acute pyelonephritis, which was evidenced by fever, frequency of urination and the finding in the urine of masses of pus cells and the colon bacillus. Ammonium chloride (4 Gm.) and ammonium mandelate (12 Gm.) administered daily for six days did not produce hemoglobinuria or an increase in hemoglobinemia. This therapy failed to decrease the p_H of the urine below 6.0 and also failed to reduce the pyuria and bacilluria. On the sixth day of this treatment progressive left hemiplegia developed, with incontinence of urine and feces. In the subsequent three months before death there occurred thrombosis of the left femoral vein, oliguria and uremia following trans-

fusion and decubitus ulcers over the sacrum. The value for nonprotein nitrogen increased to a maximum level of 230 mg. per hundred cubic centimeters sixteen days after transfusion.

Autopsy.—On gross examination the kidneys were of normal size and showed multiple small abscesses involving the cortex and tubular portions of the medulla between the pyramids. These areas were uniformly dark brown and gave a strong prussian blue reaction. The liver weighed 2,100 Gm., appeared reddish brown on section and showed a small area of recent infarction. The wall of the gallbladder was thickened. The common bile duct contained several small black calculi but was not obstructed. The spleen weighed 560 Gm. and on section revealed dark red soft pulp and a small infarct. The heart was normal. The lungs were edematous. There were fibrous pleural adhesions involving the upper lobe of the right lung. Thrombophlebitis involved the left femoral, saphenous and external iliac veins. The brain showed a large cystic area of softening involving a portion of the right internal capsule, the claustrum and a small portion of cerebral cortex. The bone marrow from the vertebrae, sternum, ribs and femurs was dark red and cellular. The tibial marrow was dark red but contained scattered areas of fat. There was a decubitus ulcer over the sacrum.

On microscopic examination the kidneys showed multiple areas of abscess formation, large deposits of hemosiderin confined to the tubular epithelium of the cortex and hemoglobin casts filling many of the collecting tubules. The liver revealed varying degrees of congestion of the central vein of the lobule, with atrophy of liver tissue and distention of the hepatic sinusoids and a moderate amount of atrophy of the hepatic cords. There were small areas of focal necrosis. The spleen contained an area of infarction and necrosis. Hemosiderosis was observed only in the kidney.

The bone marrow showed hyperplasia of the red cell series, except that from the tibia, which contained only occasional islands of hemopoietic tissue.

Case 4.—A man aged 32, an unemployed automobile mechanic, single, living in Virginia, was admitted to the Boston City Hospital in 1937.

History.—The first deviation from health occurred in 1932, when the urine on three occasions, once in March, once in August and once in November, was observed to be dark with a heavy sediment. Lack of energy, increased fatigability, palpitation and dyspnea on exertion developed insidiously during this period. Anemia was present; a count of 2,500,000 red blood cells per cubic millimeter with 50 per cent of hemoglobin was observed as early as January 1933.

As was reported in detail by Hamburger and Bernstein,[4] this patient was observed in the Johns Hopkins Hospital in 1933 and in the Memorial Hospital in Richmond, Va., each year from 1933 through 1938; splenectomy was performed at the Hospital of the University of Pennsylvania in March 1935.

Throughout this period the patient was unable to work because of fatigue, and weakness. These conditions have persisted to the time of writing. He continued to show intermittent attacks of hemoglobinuria, chronic anemia and variable icterus. Splenectomy did not reduce the anemia. A total of fifty-three transfusions of whole blood had been given up to September 1937, associated with reactions of variable severity.

During the aforementioned periods of observation the number of red blood cells varied from 1,600,000 to 2,700,000 per cubic millimeter and the hemoglobin content from 30 to 52 per cent. The reticulocyte count was constantly elevated and was as high as 39 per cent. Before splenectomy the number of white blood cells varied

between 4,050 and 9,000 per cubic millimeter; after splenectomy the level was usually higher. Serologic tests for syphilis repeatedly gave negative results, as did repeated observations of the Donath-Landsteiner reaction. The gastric juice contained free hydrochloric acid after injection of histamine. The urine continued to show hemoglobin, but the nocturnal element apparently disappeared, as has been mentioned (chart 5). Roentgen examination of the long bone revealed no abnormality. Cutaneous tests with a variety of substances were without reaction.

Various forms of treatment were without permanent benefit, namely, transfusions of whole blood, parenteral administration of liver extract, a short course of injections of neoarsphenamine, intramuscular injections of antivenin, intramuscular injections of ascorbic acid and the oral administration of desiccated hog stomach (ventriculin), iron, calcium gluconate and liver extract.

At operation (1935) the spleen weighed 360 Gm. The sinuses contained a moderate amount of blood. The splenic pulp was normal. The postoperative course was complicated by otitis media and by mastoiditis requiring mastoidectomy.

Past History.—At the age of 14 the patient had two attacks of multiple cutaneous boils. One small boil recurred in 1934. The following operations were performed: tonsillectomy in 1919; dental extractions in 1930, 1934 and 1936; adenoidectomy in 1933, and splenectomy in 1935. Before the present illness the patient had been exposed to carbon monoxide during automobile repair work and had occasionally noticed headache.

Family History.—There was no familial history of anemia, jaundice or hemoglobinuria. One sibling died at the age of 19 of Bright's disease; 3 siblings were well.

Physical Examination.—The patient was short, stocky, well developed and well nourished. He did not appear ill. The skin was of uniform brownish hue, and the scleras showed a similar brownish tint. The temperature and pulse rate were normal. The blood pressure was 108 systolic and 70 diastolic.

Laboratory Observations.—The laboratory observations concerning the blood are summarized in table 1. During two months' study the urine was never free of hemoglobin. The nonprotein nitrogen content of the blood was abnormally elevated to a maximum of 72 mg. per hundred cubic centimeters, usually varying between 45 and 64 mg. The urine contained a heavy trace of albumin but the specimens showed small amounts of hemoglobin; the sediment revealed casts and hemosiderin. The stools showed no occult blood. The Takata-Ara reaction was weakly positive. The gastric juice after injection of histamine contained 28 units of free hydrochloric acid.

Progress.—During mild hemolytic episodes the patient noted fatigue, anorexia, epigastric discomfort and indigestion. In the five years of his illness multiple transfusions of whole blood were used as the major therapy, from one to three per week being administered at intervals of from six weeks to several months. Three transfusions of 500 cc. each of citrated whole blood were given on alternate days during observation at this hospital. The maximum temperatures after the transfusions were 102.4 F., 102.4 F. and 99.4 F., respectively. The patient was in a severe hemolytic episode at the time of the transfusions and continued to show extremely elevated levels of hemoglobin in the plasma and in the urine until twenty-four hours after the third transfusion, from which time the hemoglobinemia and hemoglobinuria decreased during the subsequent five days to the lowest levels observed in two months. The red blood cell count rose from 1,710,000 to 3,550,000 per cubic millimeter and the hemoglobin content from 39 to 60 per cent after these

transfusions. The percentage of reticulocytes dropped from 10 to 3. Subjectively, the patient felt much improved. Since his discharge from this hospital the course of the disease has remained unaltered.

CASE 5.—A woman aged 30, a housewife, living in Pennsylvania, was observed for two days in Boston in November 1938.

History.—The patient's first symptoms of illness occurred in 1931, at the age of 23, in Germany, when pallor with slight jaundice developed in association with her first pregnancy. Delivery was complicated by postpartum hemorrhage, after which the level of hemoglobin was observed to be low and iron was administered. In all subsequent examinations of the blood, made each year, anemia had been present, the value for hemoglobin usually being approximately 50 per cent. A second pregnancy (in 1934) was uneventful except for the finding post partum of a hemoglobin level of 45 per cent. A transfusion at this time was followed one week later by headache, abdominal pain, nausea, vomiting and jaundice. In 1935 the removal of a sebaceous cyst was complicated by erysipelas. In 1936 the patient had two attacks of violent pain in the right upper quadrant of the abdomen, described as gallbladder colic associated with moderate jaundice. Because of anemia the patient received four blood transfusions. In April 1937 the spleen was removed. Six direct transfusions of whole blood were given, without apparent reaction. After operation the anemia continued unaltered, with intermittent moderate jaundice usually associated with an infection of the upper respiratory tract. During such episodes the patient felt fatigued and was required to rest most of the day. At other times she carried on moderate activity.

On one occasion after an infection of the respiratory tract in October 1938, the urine was grossly red. On close questioning the patient recalled other periods of several days during which the urine had been dark, but nocturnal increase had not been observed.

Various forms of treatment were without lasting benefit, namely, transfusions, intramuscular injection of liver extract and oral administration of liver extract and of iron.

Past History.—Tonsillectomy had been performed at the age of 18.

Family History.—The paternal grandfather apparently had a palpable spleen without anemia. There was no familial history of anemia, jaundice or hemoglobinuria.

Physical Examination.—The patient was well developed and well nourished. She appeared pale and slightly jaundiced. The temperature and the pulse rate were normal. The blood pressure was 110 systolic and 70 diastolic. The edge of the liver was palpable on deep inspiration.

Laboratory Observations.—The laboratory observations concerning the blood are summarized for the years 1937 and 1938 (table 1). Two specimens of urine observed at this hospital on November 18 were dark red, containing large amounts of hemoglobin (without red cells) and a heavy precipitate of hemosiderin. At this time free hemoglobin was observed in the plasma. There was no opportunity to observe the influence of sleep. In previous examinations the specific gravity of the urine had varied from 1.012 to 1.023. The urine showed a heavy trace of albumin and occasional red blood cells. The urine was amber. The stools contained no occult blood. The basal metabolic rate was —4 per cent. The gastric juice contained a normal amount of free acid. Drainage of the biliary tract revealed no abnormality. Roentgen examination showed no abnormality of the chest, gastro-

intestinal tract, gallbladder, kidneys or ureters. At operation in 1937 the liver and gallbladder were normal and the spleen weighed 260 Gm.; microscopically the spleen showed no increase in pigment and only a slight deviation from normal in the prominence of reticulum cells in germ centers.

Dr. William B. Castle and Dr. John H. Dingle made important suggestions. The observations on porphyrins are the work of Dr. Robert Kark. Miss Constance Brooks gave technical assistance. Observations of the hydrogen ion concentration of blood and of the carbon dioxide and oxygen content of blood were made by permission of Dr. David B. Dill by his associates Dr. Jost Michelson and Dr. C. Daly of the Fatigue Laboratory, Harvard University. Study of the patient in case 4 was by permission of Dr. William B. Porter, Richmond, Va.; the data in case 5 were supplied by Drs. Thomas Fitz-Hugh Jr. and William U. McClenahan, Philadelphia.

DIAGNOSIS OF HYPERSENSITIVENESS TO THE BEE AND TO THE MOSQUITO

WITH REPORT ON SUCCESSFUL SPECIFIC TREATMENT

ROBERT L. BENSON, M.D.
PORTLAND, ORE.

The animals which are harmful to man include a wide range. The predatory mammals which choose man as an article of diet are referred to mainly in writings on adventure. As one descends to the Reptilia, however, one finds much written on the venoms of snakes and other members of this group. Still farther down the scale come the Arthropoda, including, besides the spiders, scorpions, ticks and other arachnids, the immense and fascinating array of insects about which countless volumes have been contributed to scientific libraries. As one proceeds downward through the predatory worms, one comes to the lowest of all, the Protozoa, important agents of harm, either through their own activity or by collaboration with insects or higher animals.

The present consideration will be confined entirely to the class Hexapoda, or insects, which includes, according to various entomologists, thirty or more orders. Of these I need mention only a few, together with important examples. Anoplura (sucking lice), Hemiptera (true bugs), Trichoptera (caddis flies), Lepidoptera (moths), Diptera (flies and mosquitoes), Siphonaptera (fleas) and Hymenoptera (bees, wasps and ants) embrace most of the genera which interest physicians.

The study of allergy is probably not concerned with the role of insects as primary or secondary hosts for numerous human parasites, including Vermes, trypanosomes, Protozoa, lower plant forms and unknown viruses. These belong to the fields of bacteriology and parasitology. Neither does this study include the essential effects of venoms and poisons. These assume importance only as they carry with them sensitizing substances, either from the insect itself or by contamination.

A knowledge of entomology is essential to a real understanding of the harmful effects of the insects. Of the works consulted one of the

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From the Department of Medicine, University of Oregon Medical School.

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most instructive has been Snodgrass'[1] volume in the Smithsonian Institution Series, which, without being encyclopedic, contributes much valuable information on the life habits of the class. Other works consulted included Snodgrass'[2] book on the honeybee, Matheson's[3] on mosquitoes and the book "Insects" in the Western Nature Study Series.[4] Several other general publications on entomology were found useful.

The insects which produce allergic phenomena may be divided into three groups according to whether they sensitize the human host (1) innocently, by scales or dust shed from the wings or body, (2) by injection of venom through the sting situated in the rear extremity, or (3) by instillation of salivary secretion through the mouth parts. Each of these will be considered. The first group includes chiefly certain nonpredatory orders, especially Lepidoptera (moths and butterflies), Trichoptera (caddis flies) and Ephemerida (May flies). The second group includes various stinging members of Hymenoptera, notably the bees, wasps and ants. The third group embraces a wide range of blood-sucking pests, chiefly among the orders Anoplura (sucking lice), Hemiptera (true bugs), Diptera (flies and mosquitoes) and Siphonaptera (fleas).

Nearly all insects have the same essential mouth parts, but with marked variations. The parts consist of the labrum (upper lip), the mandibles (upper jaw), the maxillas (low jaw) and the labium (lower lip). They may, as in the Lepidoptera, be fashioned into a siphon for sucking nectar, or they may be employed, as with many species, for chewing food, but in the predatory group they are rearranged to form a piercing needle for drawing blood.

The accompanying diagrams of the mosquito (fig. 1) will serve to illustrate the mouth parts of most blood-sucking species. The proboscis is a slender hollow needle formed by close apposition of the mandibles, maxillas, labrum and hypopharynx. Body lice have a piercing and sucking mouth for drawing blood. Fleas likewise have an oral tube for piercing the skin, and the stable fly has a short broad proboscis formed by the usual combination of mouth parts. In the bedbug and other Hemiptera the mandibles and maxillas form piercing stylets enclosed in a tube formed chiefly by the labrum.

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1. Snodgrass, R. E.: Insects: Their Ways and Means of Living, New York, Smithsonian Institution Series, Inc., 1930.

2. Snodgrass, R. E.: Anatomy and Physiology of the Honey-Bee, New York, McGraw-Hill Book Company, 1925.

3. Matheson, R.: A Handbook of the Mosquitoes of North America, Springfield, Ill., Charles C. Thomas, Publisher, 1929.

4. Pickwell, G., and others: Insects, Natural Science Department, California State Teachers College, Western Nature Study Series, Los Angeles, Suttonhouse, Ltd., Publishers, 1933.

The Hymenoptera which threaten man and animals by their sting have an anatomic setup designed for their special needs. The mouth parts are usually inoffensive and adapted to lapping nectar or chewing pollen and other foods. The stinging mechanism, situated in the rear end of the animal comprises an elaborate offensive and defensive apparatus (fig. 2) formed by the adaptation of the ovipositor. Through its hollow double lancet is injected the venom, a highly complex mixture of chemical ingredients, the probable nature of which in the bee has been considered in a previous report.

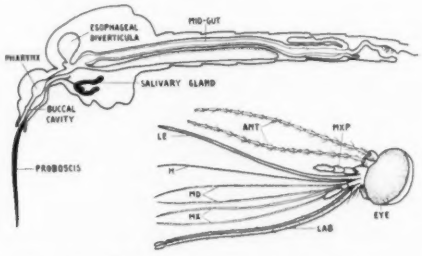

Fig. 1.—The mouth parts of the mosquito.

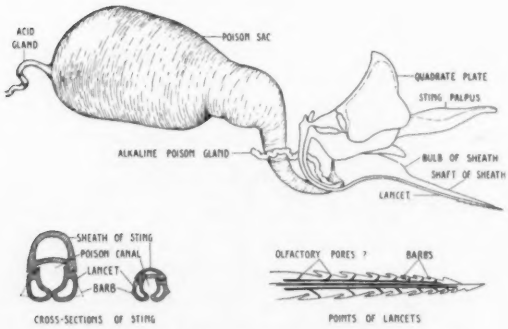

Fig. 2.—The stinging mechanism of the honeybee.

I. INHALATION OF EMANATIONS FROM INSECTS

Coca and his associates [5] stated that Ancona, in 1922, described an epidemic asthma which, at certain times, occurred among cereal workers in Italy as a result of handling grain infested with the larvae of Pediculoides ventricosus and that Van Leeuwen reported a similar condition in Holland. Coca, however, regarded these reactions as nonspecific.

5. Coca, A. F.; Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., Charles C. Thomas, Publisher, 1931.

In 1929 Parlato [6] reported an instance of rhinitis and asthma due to the emanations of the sand fly, or caddis fly, an insect of the order Trichoptera abounding along Lake Erie and the Niagara River. The following year, in a routine study of 192 allergic patients,[7] he found that 14 reacted to filtered extracts of the same species by intracutaneous and ophthalmic tests. Passive transfer by the Prausnitz-Küstner technic was successful in the 4 cases in which it was tried. At about the same time Figley [8] recorded 4 cases of asthma due to the pellicles shed by the May fly, a member of the order Ephemerida which swarms about Toledo, Ohio.

In 1929 Sternberg [9] described the occurrence of asthma caused by Cimex lectularius (bedbug). Unfortunately no proof was available that sensitization arose from inhalation. Successful transfer by the Prausnitz-Küstner method with 1:1,000 extracts of the bug did, however, suggest the inhalation route. Such a high grade of sensitiveness is not usually observed when the allergic reaction arises from the bite. This point will be considered more extensively later.

Equally difficult to classify were the two cases reported by Ellis and Ahrens [10] of reactions to emanations of bees. The first patient was definitely sensitive by scratch to venom, extracts of various portions of bees' bodies and pollen from hives, but not to ordinary pollen, wings of bees or stings. These apparent disagreements were difficult to explain. The second patient gave a history of asthma from the airborne products of the bee and also of sensitiveness to the sting. The findings in this case were inconclusive because of the patient's refusal to submit to adequate testing.

As might be expected, the Lepidoptera (moths), with their dust-laden wings, proved to be a cause of inhalation symptoms. Parlato [11] in 1932 described in detail the abundant dust shed by the wings of moths and reported an instance of hypersensitiveness. Later he announced passive transfer of the reagins of the caddis fly, butterfly and moth and found only a quantitative difference in the degrees of

6. Parlato, S. J.: A Case of Coryza and Asthma Due to Sand Flies (Caddis Flies), J. Allergy **1**:35, 1929.

7. Parlato, S. J.: The Sand Fly (Caddis Fly) as an Exciting Cause of Allergic Coryza and Asthma, J. Allergy **1**:307, 1930.

8. Figley, K. D.: Asthma Due to the May Fly, Am. J. M. Sc. **178**:338, 1929.

9. Sternberg, L.: A Case of Asthma Caused by the Cimex Lectularius (Bedbug), J. Allergy **1**:83, 1929.

10. Ellis, R. V., and Ahrens, H. G.: Hypersensitiveness to Air Borne Bee Allergen, J. Allergy **3**:247, 1932.

11. Parlato, S. J.: A Study of the Atopic Reagins of the Caddis Fly, Butterfly and Moth, J. Allergy **3**:125, 1932.

reactivity to extracts of the three types of insect. Balyeat and his associates [12] also reported routine reactions to extracts of Lepidoptera.

The only reference to nasal allergy from emanations of the house fly's wing is that of Jamieson.[13] His patient reacted to scratch and to nasal instillation. Passive transfer was successful.

II. SENSITIZATION TO STINGS OF HYMENOPTERA

In a previous publication Semenov and I [14] reported an instance of extreme hypersensitiveness to the sting of the honeybee, presented a résumé of the more important literature and gave a detailed description of the bee's stinging mechanism and the reputed components of the venom. I have subsequently encountered other examples of sensitization to Hymenoptera which I shall recite briefly.

It is apparent that extreme reactivity to these insects is an acquired condition. In reporting our first case we mentioned that the patient was a bee keeper who during his first year in the business suffered many stings, reputedly as many as seventy-five in one day, with no unusual harm. During the second year he began to experience increasing distress with each sting, and by the end of the third year he became so ill after single stings that he feared having to abandon his occupation.

In the meantime Beck [15] presented his interesting plea for the venom therapy for rheumatic conditions, but admitted a lack of knowledge as to the method followed in the preparation of the antigen. Of especial concern to us, however, was his recital of numerous minor or major casualties from stings of Hymenoptera, including information from lay sources and even from the daily press. In spite of the variable and sometimes doubtful source of data the author presented a commendable volume of detail.

It was easy to explain his reported death of an imbecile following stings so numerous that bees were passed by emesis and from the rectum and also the death of a man of 84 who received 1,200 stings. His numerous instances of death from a single sting suggested anaphylaxis, but the theory lacked experimental proof. Much more interesting were his many accounts of increasing sensitivity with repeated stings and his reported cases of generalized urticaria, sometimes bullous. He also related examples of anaphylactic shock from isolated stings.

12. Balyeat, R. M.; Stemen, T. R., and Taft, C. E.: Comparative Pollen Mold, Butterfly and Moth Emanation Content of the Air, J. Allergy **3**:227, 1932.

13. Jamieson, H. C.: The House Fly as a Cause of Nasal Allergy, J. Allergy **9**:273, 1938.

14. Benson, R. L., and Semenov, H.: Allergy in Its Relation to Bee Sting, J. Allergy **1**:105, 1930.

15. Beck, B. F.: Bee Venom Therapy, New York, D. Appleton-Century Company, Inc., 1935.

Necessarily these reports, like all the reports of death in the literature, lacked immunologic verification and left the exact cause of death in doubt.

An adequate demonstration of specific sensitization to the sting of the bee must rest on the essential relation of antigen and antibody. Braun [16] reported successful inoculations of increasing doses of material from bees in a patient who reacted to the sting of the insect, but unfortunately failed to obtain verification by cutaneous or other specific tests. Previous to our original report there was a dearth of evidence of definite reaction to extracts of bees followed by specific relief. I therefore decided to review once more the factors in hypersensitiveness to bees and other species of insects and to supply additional examples.

Our previous report mentioned that the specific harmful effects of the Hymenoptera should be considered as possible results of sensitization to the venom itself, to pollen adherent to the bee's body or to allergens inherent in the insect. To these I shall now add atopic reactions due to inhalation of material shed by the bee. This conception has already been discussed in connection with the report of Ellis and Ahrens.[10]

The venom of bees and other members of the Hymenoptera contains a complex poison which Wells,[17] on the basis of Flury's [18] study, interpreted as a possible combination of lecithin with basic radicals somewhat resembling sapotoxins and cantharidin. Whatever the chemical nature of the poison may be, it is of moderate toxicity to the human species, nonspecific and therefore tending to cause somewhat of a reaction in every one. The ordinary clinical symptoms appear in various works on medicine and toxicology. I am especially concerned here with the alarming and even fatal manifestations, which are tabulated in a book such as Beck's. It is obvious that a multiplicity of simultaneous stings might provide enough true poison to cause death. When, on the other hand, a person who has previously withstood repeated attacks of bees without harm later succumbs to the effect of a single sting, it is difficult to reject the suspicion that one is dealing with a specific phenomenon in sensitization.

The question whether venom itself can sensitize is obscured by a consideration which Wells [17] raised. He ascribed a histamine-like action to the venom of bees. Semenov and I [14] compared the effects of bee venom and of histamine on a strip of the virgin guinea pig's uterus. The

16. Braun, L. I. B.: Notes on Desensitization of a Patient Hypersensitive to Bee Stings, South African M. Rec. **23**:408, 1925.

17. Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1925.

18. Flury, F.: Ueber die chemische Natur des Bienengiftes, Arch. f. exper. Path. u. Pharmakol. **85**:319, 1920.

strip of muscle responded to a solution of 1 part of bee venom in 100,000 parts of saline solution, and the tracing thus obtained corresponded closely with that given by histamine. It seemed highly probable that bee venom contained a substance resembling histamine. Considering the similarity of the effects of histamine and of anaphylactic bodies, the implications became still more confusing and the need of painstaking immunologic study appeared obvious.

In my study with Semenov we compared in a highly sensitive person the cutaneous scratch reactions to bee venom, the stinging apparatus and the substance of the bee's body. It developed that an extract of bee's bodies from which the stingers and poison sacs had been removed caused a reaction as strong as that to the insect's stinging mechanism or even the venom itself. The three effects were identical: 4 plus immediate wheals, as compared with scant 2 plus wheals with a 1:1,000 solution of histamine. Nonsensitive controls gave only a negligible reaction to the three products of the bee, but showed the usual nonspecific reaction to histamine.

After a repetition of such experimentation, we concluded that the patient was definitely sensitive to extracts of the bee. This hyperreactivity was not due merely to the histamine-like effect of the venom, since the extract of the body without the poison apparatus produced the same wheal. Concentration of extracts with cold alcohol or a saturated solution of ammonium sulfate, to increase the percentage of protein, augmented the reactivity. Inoculations of such concentrates over an extended period resulted in a complete cessation of serious effects from multiple stings. We felt justified in concluding that the patient's sensitive state was due, not to the poison of the venom proper, but to the included body protein of the insect. In the seven years since publication of these results, an additional immunologic study has been conducted to clear up certain doubtful points. Coca [5] made the very just criticism that passive transfer was needed. It also occurred to me that attention should have been given to the delayed reactions as well as to the early wheals. The possible role of pollens also demanded more study. The 10 additional cases here recorded will throw some light on these and on other problems.

All the patients were selected because they complained that stings produced large, hot, painful swellings which persisted for days, sometimes with general prostration. In 5 of them a sting constituted a definite hazard to life. The seventh patient's father, who was an agent for a pharmaceutic house, saw his son stung and described the onset of profound shock. He maintained that prompt administration of epinephrine alone prevented a fatal outcome.

The accompanying table includes, besides data on patient 1, previously described, data on the 10 additional patients subjected to immunologic study.

Data on Eleven Patients Subjected to Immunologic Study

No.	Name	Sex	Age When Tested	Reaction to Inoculations			Degree of Clinical Sensitization	Sensitization to Pollens	Other Allergic Reactions	Clinical Diagnosis	Treatment for Bees
					Immediate	24 Hr.					
1	E. S.	M	50	Bee Mosquito	++++ —	.. ..	Prostration, pulmonary symptoms simulating pneumonia	Strong	None	Hay fever, allergy to bees	Course of inoculations of bee extract, with complete relief, 1929-30
2	J. W.	M	32	Bee Hornet	++++ —	.. ..	Large and persistent swelling	Strong	None	Hay fever, allergy to bees	None
3	C. W.	F	19	Bee Hornet Mosquito	++++ ±+++ +	.. .. ..	Large and persistent swelling	None	Many foods and dusts	Asthma, allergy to bees	None
4	I. E. W.	F	44	Bee	++++	..	Large and persistent swelling	Moderate	Hay, flaxseed, mustard, etc.	Asthma, allergy to bees	None
5	W. C. H.	M	6	Bee	++	++++	Large and persistent swelling, urticaria, dyspnea	Negligible	Not tested	Allergy to bees	8 inoculations of bee extracts, 1935; stung 1937-1938, with ordinary small wheal resulting
6	H. W. G.	M	49	Bee	++++	++++	Large and persistent swelling	Extreme	Many foods and dusts	Hay fever, vasomotor rhinitis, allergy to bees	None
7	A. W.	M	13	Bee Hornet	++++ —	++++ ..	Extreme prostration, anaphylactic shock?	None	Not tested	Allergy to bees	14 inoculations of bee extract, 1934, and 9 in 1937; no subsequent stings
8	G. L. H.	M	63	Bee Hornet Mosquito	++++ ±+ ++++	++++ ++++ —	Large and persistent swelling	None	Many foods	Urticaria, allergy to bees	3 inoculations of extract of Hymenoptera; no subsequent stings
9	L. W.	M	34	Bee Yellow jacket Hornet	++++ ± ±	++++ — —	Persistent large swelling with malaise and prostration; later sloughing at site of sting	None	Epidermals, house dust	Urticaria, eczema, headaches, allergy to bees	One season's inoculations of bee extracts; no subsequent report
10	C. F. R.	M	62	Bee Hornet Yellow jacket	++++ + ±	++++ ± ±	Collapse with unconsciousness for 5 minutes followed by urticaria	None	Not tested	Allergy to bees	One season's inoculations of bee extracts; no subsequent report
11	E. M.	F	62	Bee Vespula wasp Mosquito	++++ ++++ +++	++++ ++++ +	Extreme and persistent swelling	Moderate	Not tested	Allergy to bees, dermatographia	7 inoculations of bee extract; no stings reported

Of the 11 patients, 5 consulted me because of the hazard attending an extremely violent response to single attacks of bees. It was my belief that these belonged probably in the same category as the subjects of unexplained death due to shock from single stings, as reported by Beck.[15] I therefore undertook to inoculate them repeatedly with bee extracts according to the technic formerly described.[14] In the previous report appeared a full description of the treatment of patient 1, a bee keeper who was dangerously sensitive to a single sting. After a course of inoculations for three months, he received on one occasion at least twenty-five simultaneous stings with no ill effects beyond local discomfort. On a subsequent occasion I personally observed the site of a sting which the patient had received a few hours before on the canthus of the eye and found no significant infiltration. I treated him only two seasons, but in the subsequent ten years he reported no serious consequences from stings. Patient 5 in 1935 received a course of eight inoculations. The following report received recently from his father, who is professor of pathology at the University of Oregon Medical School, indicates the apparent relief obtained:

> Until the summer of 1937 my son escaped contacts with bees, so that there was no opportunity to learn the results of your desensitization treatmet given in 1935. He was then stung by a honeybee with no more effect than a local reaction at the site of contact. The extreme allergic manifestations which he formerly had were entirely absent. Again in 1938 he received a sting without untoward result. I am most grateful to you for the striking results of the treatment given.

The other violent reactor, patient 7, and the casual reactor, patient 8, have been treated but the efficacy is still to be determined. I do not yet feel justified in deliberately subjecting any of these subjects to the onslaughts of bees. As a result of the limited experience to date I feel confident, however, that the specific inoculations will prove a safeguard against the occasional alarming consequences of stings.

Of more import here are certain immunologic findings. Venom caused no stronger reaction in any of these sensitive patients than did the extracts of bees' bodies from which the stings and poison sacs had been removed. Thus patient 1, by the scratch test, gave 4 plus reactions to raw venom, to extracts of stings and poison sacs combined and to extracts of bees' bodies from which the poisonous rear ends had been removed. Patient 2 gave 4 plus reactions to extracts of bee stings and poison sacs combined, of whole bees' bodies and of bees' bodies from which the stings and poison sacs had been removed. All the other patients responded similarly. It seemed logical to conclude that in these allergic persons the specific phenomenon was due to some allergen inherent in the insects' bodies and that the sting caused sensitization only because its venom included, besides its ordinary poison, the identical allergen of the bees' protoplasm.

The nature of this antigen was further studied. I used many thousands of honeybees in the preparation of materials. The stings and poison sacs were plucked from one group, the remaining portions of the bodies being reserved for separate study. In another group the whole bees were used. In all instances the material was ground, dried, etherized to remove fats, extracted in physiologic solution of sodium chloride and subjected to the procedures ordinarily employed in making protein, namely, precipitation with cold alcohol or a saturated solution of ammonium sulfate. The resulting impure protein was washed repeatedly with cold alcohol and ether and dried to form a powder. Dialysis was of course used for ammonium sulfate precipitates. The resulting dry antigen formed the basis of most of my extracts. It was not necessary to assume that this fraction represented anything corresponding to pure protein. It was found, however, that the process of concentration increased the protein content of extracts and enhanced their potency. I became convinced that I had, in an impure form, a protein-bound antigen of the bees' bodies which was specific, nondialyzable, thermostable and responsible for the type of violent phenomena which occasionally result from the sting of a single insect of the order Hymenoptera.

Pollen adherent to the bee might, through inhalation, account for certain symptoms in bee keepers, but could scarcely apply to the effects of stings with which I was dealing. The lancet of the bee carries no pollen with it; yet the tests proved conclusively that the stinging apparatus caused reactions as potent as those caused by the bees' bodies. More important still, 5 of my 11 patients were found nonsensitive to any of the pollens of the vicinity. I was forced to the conclusion that the allergen resided in the substance of the insects' bodies.

Most of the patients whose data were tabulated had, in addition to their specific response to the products of the bee, a definite atopy to foods or dusts or both. Clinically 3 had hay fever, 2 asthma and 1 urticaria. For some of them the routine of handling the atopic condition was so burdensome that I found it impossible to include a course of inoculations for bees.

The advantages of the intracutaneous testing became obvious when, in cases 5 to 11 inclusive, I supplemented the scratch test with this method. The early wheals were usually more pronounced than those following the scratch, but the chief advantage of the injection was that it produced delayed infiltrations which were red, warm, raised and painful and which persisted for days. I found that these were even more significant than the immediate reactions. Thus, patient 5 showed only a 2 plus wheal from the scratch and even from intracutaneous injection of 0.05 cc. of a 1:25 solution of extract of bee. The next day, however, at the site of injection there was a large, hot, itching swelling

which persisted for three days. In patient 6 the twenty-four hour infiltration was even more pronounced, occupying about one half of the flexor surface of the whole arm. In patient 8 both whole bee protein and stingerless bee protein, injected intracutaneously, caused large 4 plus wheals in fifteen minutes, and they increased greatly in another thirty minutes. The wheals next day were red and tender and measured 50 by 50 mm. for the whole bee protein and 60 by 60 mm. for the stingerless bee protein. All these late infiltrations were in general similar to those described for the mosquito (fig. 3).

Passive transfer by the Prausnitz-Küstner technic has proved difficult and was omitted from our earlier report.[14] After unsuccessful attempts with several serums, I found that the serum of patient 6 was the only one which contained sufficient reagin for transfer. Of this

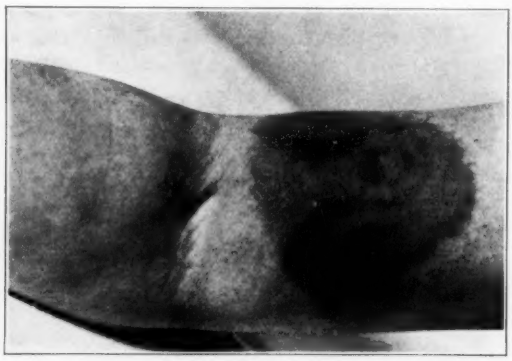

Fig. 3.—Twenty-four hour reaction to intracutaneous inoculation of a 1 : 50 dilution of the concentrate of the mosquito Aedes vexans in patient 4.

serum I injected 0.1 cc. into each of two sites on a nonreactive subject. Two days later site 1 received 0.02 cc. of a 1 : 50 solution of the extract of bee's sting apparatus and site 2 received a similar amount of extract of hornets of about the same titer. Control sites received equal amounts of the same antigens. Within fifteen minutes the site of the bee extract showed an irregular wheal measuring 14 by 11 mm., while its control failed to react. At the site of the hornet extract appeared a wheal measuring 16 by 11 mm., with a negligible reaction in its control. This experiment furnished ample evidence that the serum of this strongly reactive patient contained reagins for both the honeybee and the hornet. The twenty-four hour reaction failed to transfer.

One has therefore a single instance of passive transfer of the immediate reactions to the bee and to the hornet. The failure of other serums to cause the same phenomenon convinces me that hypersensi-

tivity to the Hymenoptera is not dependably transferable. This is not surprising in view of the fact that the important reaction reaches its maximum intensity in twenty-four to forty-eight hours. It is quite possible that one is dealing here with a distinct type of allergy which will exhibit the Prausnitz-Küstner phenomenon only as far as pronounced immediate wheals are concerned.

Sensitization to bees is, however, unquestionably a specific phenomenon. The foregoing successful passive transfer of the reaction to both the honeybee and the hornet by the same serum raised the question whether this patient had a group sensitivity to different Hymenoptera or whether he was independently sensitive to the two insects. Was it a species specificity toward each or a specificity toward the whole order? This question requires further study. Suffice it that 4 of my bee-sensitive patients (2, 7, 9 and 10) failed to react to the hornet and wasp, while 3 others (3, 8 and 11) showed the same 4 plus reaction to the bee and the hornet-wasp group. It is of interest in this connection that Ellis and Ahrens [10] reported coincident reactions to honeybees and bumblebees.

In the meantime reports appeared on allergy to wasps and hornets. Hubert [19] and Mantoux [20] published such reports without corroborative tests. Lincoln [21] recently described an interesting example of acute shock from seven stings of yellow jackets but included no immunologic studies.

Sulzberger, in discussing my earlier paper [22] on the mosquito, stating that the twenty-four hour reaction, but not the immediate reaction, was abolished by reinjection in the same site, said:

> You can desensitive patients with comparative ease as far as the late twenty-four to forty-eight-hour papular reactions are concerned; whereas the immediate or wheal type reactions, although also due to hypersensitivity, are extremely difficult to influence and usually remain constant in spite of all desensitizing procedures.

With this statement I am in full accord.

Patient 7, who had a 3 plus wheal from 0.02 cc. of a 1:25 solution of the extract of whole bee, reacted on the following day with a 4 plus infiltration which measured 14 by 9.5 cm. and was hot, red and swollen. Three days later, when the reaction had subsided, he received a reinoculation in the same site with 0.05 cc. of the same antigen. The

19. Hubert, E.: Accidents anaphylactiques par deux piqures de guêpe reçues à une heure d'interval, Lyon méd. **138**:678, 1926.

20. Mantoux, C.: Choc par piqure de guêpe, chez un tuberculeux, Presse méd. **36**:259, 1928.

21. Lincoln, M.: Severe Alleregic Reaction Following Wasp Stings with Subsequent Relief of Chronic Arthritis, J. Allergy **7**:372, 1936.

22. Benson, R. L.: Diagnosis and Treatment of Sensitization to Mosquitoes, J. Allergy **8**:47, 1936.

immediate reaction was slightly larger than the original immediate reaction (fig. 4), but on the following day no delayed reaction was present. The original injection failed to abolish the immediate wheal but completely abolished the reactivity locally as far as the much larger late reaction was concerned. This result corresponded with what I formerly reported for the mosquito. It also supported the hope that a sufficient number of inoculations with increasing doses might eventually abolish the large and distressing infiltration in extremely bee-sensitive patients.

CONCLUSIONS BASED ON PARTS I AND II

1. Inhalants consisting of desquamations of moths, caddis flies, May flies or bees belong in one group and may contain sensitizing atopens comparable to epidermal proteins or pollens.

2. More important in regard to bees and other Hymenoptera is the sensitization of certain persons following repeated stings.

3. The venom of Hymenoptera contains a nonspecific poison of complex composition which is apparently not the true antigen for sensitive persons.

Fig. 4.—Immediate wheals. *A*, the reaction to whole bee protein, 0.02 cc. of a 1:25 solution; *B*, the reaction to stingerless bee protein, 0.02 cc. of a 1:25 solution; *C*, the reaction to whole bee protein, 0.05 cc. of a 1:25 solution in the site of a previous similar inoculation.

4. In the stinging act the venom carries with it a minute amount of antigen peculiar to the bee's body and capable of sensitizing the person.

5. This antigen is present throughout the bee's body and is independent of venom or pollens.

6. The antigen reacts in the sensitive person (*a*) by immediate wheal and (*b*) by a more violent delayed reaction which is large, hot, red and swollen and which persists for one to several days.

7. The antigen is species specific or in some instances order specific. Further study is required on this phase of the subject.

8. The antigen is apparently protein bound, nondialyzable, thermostable and specific.

9. Passive transfer, though difficult, is possible, as was demonstrated with one sensitive serum in regard to the immediate reaction but not to the delayed reaction.

10. Reinoculation in a previous inoculation site can demonstrate desensitization in regard to the large twenty-four to forty-eight hour infiltration, but not to the immediate wheal.

11. The meager studies thus far conducted offer great hope that repeated inoculations of sensitive persons with increasing doses of extracts of bees will eventually reduce the violent reaction to these insects below the danger level. Two completely successful results of such inoculations were reported.

III. SENSITIZATION TO BITING AND SUCKING INSECTS

Among biting and sucking insects belongs the large group of relatively predatory insects of several orders which obtain their nourishment by sucking the blood of animals much larger than themselves. Some prefer rodents or other small mammals and accept man as a second choice. They are helpless as far as rear end weapons of defense are concerned, usually employ their intricate mouth parts only for sucking or chewing food and retreat promptly if detected in their poaching.

Most of the biting insects are by nature relatively nonpoisonous. The tarantulas, scorpions and black widow spiders have, to be sure, definite poison, but these belong to a distinct branch of Arthropoda, the arachnids. The predatory insects in the act of biting or sucking inject some of the secretion of the salivary glands situated in the thorax, and this fluid, of variable and incompletely known composition, may result in certain blemishes of the skin which require discussion here.

The observations of Kemper [23] on the bites and secretions of certain insects are of interest. Referring to the bedbug, he stated that the size and character of the welt resulting from the bite are independent of the size of the attacking insect. The youngest larvae cause as strong reactions as the mature insects. Nor does it matter whether the feeding continues undisturbed or is interrupted. Not only with bedbugs but with other biting insects, he contended, the injection of saliva immediately follows the insertion of the proboscis and often precedes the initiation of the sucking act. It was found possible for the bedbug to produce a succession of many bites because of the extremely minute volume of secretion voided in each. Kemper estimated, with the aid of a microscope, that the total storage of saliva was not more than 0.18 cc. and cited the still more impressive figures of Hase. The latter author, also on a microscopic basis, decided that the saliva injected in ten seconds of feeding aggregated 0.0000167 cc. for the bedbug and 0.0000416 cc. for the dog flea. The mosquito also, when interrupted in drawing blood, may move on to a succession of new sites, each requiring its quota of saliva. Collection and measurement of the secretion voided by this insect at each bite were not possible, but the volume was surmised to be correspondingly infinitesimal.

23. Kemper, H.: Beobachtungen über die Wirkung von Insektenstichen, Arch. f. Dermat. u. Syph. **161**:127, 1930.

Sulzberger, in the discussion previously cited, emphasized that what is regarded as "the ordinary wheal reaction to the bite of the mosquito is probably not due to the action of a secreted irritant but is probably in most instances attributable to an acquired and specific sensitization." This statement and subsequent reading pointed to the necessity of considering, in addition to the high grades of sensitiveness to insects which I have previously described, the ordinary early wheals and later papules which customarily arise from bites. It would then be possible to compare the more violent effects of insects, particularly the mosquito.

Hecht [24] said that it was not rare to find persons who gave no reaction to the bites of insects. In fact, he himself had such an immunity to the bite of the bedbug and even failed to incite reactivity to the insects in a circumscribed area of his skin by allowing them to feed there repeatedly over prolonged periods. Kemper [23] found that among 45 persons tested 8 were immune to the bites of bedbugs. On one nonreactive person he allowed fully 10,000 bedbugs to feed for a period of twenty-five months without breaking down the immunity. Hase [25] also, as early as 1917, maintained that certain persons had either natural or acquired freedom from reaction to the bite of the bedbug.

Hecht [24] stated that Hase, Sikora and Martini made independent reports on immunity to the body louse. Of especial interest in this connection was the example reported by Peacock,[26] who was an entomologist with the American Red Cross Trench Fever Commission in France in 1918. Several volunteer subjects received intravenous injections of filtered extract of the excrement of lice. Fifteen minutes after injection one volunteer showed marked anaphylactic phenomena with severe edema of the face, general urticaria and great discomfort. The symptoms slowly subsided. This subject had previously been used in a study in which over 100 normal lice fed on him during a period of eleven days. This experiment furnished evidence of early tolerance and a later acquired sensitization of high grade.

As early as 1912 Boycott,[27] working with fleas, decided that ordinary persons who reacted to the bite of common fleas (Pulex irritans) failed to react to the first experimental bite of the rat flea (Ceratophyllus fasciatus) or the tropical rat flea (Xenopsylla cheopis), but later acquired sensitiveness to the bites. The same author,[28] after fourteen

24. Hecht, O.: Hautreaktionen auf die Stiche blutsaugender Insekten und Milben als allergische Erscheinungen, Zentralbl. f. Haut- u. Geschlechtskr. **44**: 241, 1933.

25. Hase, A.: Die Bettwanze (Cimex lectularius L.), ihr Leben und ihre Bekämpfung, Berlin, P. Parey, 1917, p. 137; cited by Hecht.[24]

26. Peacock, A. D.: The Reaction to Flea Bites: Anaphylaxis and Louse Infestation, Nature, London **118**:696, 1926.

27. Boycott, A. E.: The Reaction to Flea Bites, J. Path. & Bact. **17**:110, 1912.

28. Boycott, A. E.: The Reaction to Flea Bites, Nature, London **118**:591, 1926.

years, retested one of these original experimental subjects (his wife), who had previously become sensitized to Xenopsylla, to determine whether she would react to the rabbit flea (Spilopsyllus cuniculi). Nothing resulted from the first bites. In another two months, however, she had become sufficiently sensitized to exhibit red papules seven days after the feeding. By successive bites the time of latency decreased to thirty-six hours.

Boycott [29] subsequently performed a similar experiment with an imported oriental species of sand fly (Phlebotomus papatasii) which was not found in his country. He subjected 5 persons to the bites and the only one who responded had previously encountered the insect in the Orient. With repeated exposures the other 4 became sensitive within periods ranging from seven to twelve days. In contrast with these instances of acquired reactivity to lice, fleas and sand flies, Hecht [24] emphasized the difficulty of producing such a result with bedbugs.

More discouraging still were the attempts to remove the sensitization to the ordinary effects of insects. Hecht [24] stated that Pick found bedbugs more difficult in this regard than clothes lice. Little more hopeful was Hase's verbal communication to Hecht that he had only partially succeeded in desensitizing an isolated site of his skin by repeated bites of the bedbug. Hecht also cited Kemper's observation that certain persons became less reactive to species of Aedes after being excessively bitten on repeated occasions. Less encouraging, however, was Martini's report, also cited by Hecht, that after allowing numerous yellow fever mosquitoes (Aedes fasciatus) to feed for several weeks on the same area of his skin he observed no diminution of reactivity. Even Kemper's [23] successful and progressive desensitization to bedbugs performed on an area of his own skin over a period of eleven months proved transient. After a resting period of four weeks the responsiveness to bites returned. It seemed to be the consensus that attempts to abolish the ordinary cutaneous effects of insects were relatively futile. Hecht [24] grouped the ordinary reactions to insects as follows:

1. Entire nonreactivity; no antibody; no cellular ability to form antibodies readily.

2. Delayed papular reaction. The antibody introduced by the bite stimulates cellular antibody production. The residual antigen reacts with the newly formed antibody.

3. Late wheals arising similarly to the papules of type 2.

4. Immediate wheal. The cells have sufficient antibody to react to the bite, but the blood serum contains none for the passive transfer.

5. Immediate wheal and positive transfer; antibody in the cells and also free in the blood.

29. Boycott, A. E., cited in Reaction to Insect Bites, Lancet **2**:1253, 1928.

6. Complete nonreactivity. There is much free antibody present, so that, as in true antitoxic immunity, this combines with the antigen before it can participate with the cellular antibody in giving a tissue reaction.

Throughout the work cited the reactions represented in general the ordinary everyday effects of bites on average persons. The lesions were usually small and consisted of an early wheal and later papule, with or without surrounding erythema. Hecht [24] admitted that there was no definite evidence for an identity between urticarial and papular eruptions. He succeeded with some difficulty in the passive transfer of sensitivity toward bedbugs to a previously nonreactive person. Only one serum of four tried gave a successful transfer, and even with this one the site remained sensitized but a few days. The wheal alone transferred, and attempts with the late papule failed.

Martini's results, cited by Hecht, argued strongly for an immunizing process. While working with a mosquito of the genus Aedes he found the reactions smaller in the newborn and also in adults who had been bitten excessively. This observation furnished a strong indication of beginning tolerance in the newborn, later sensitization to the insects' stings and possibly final specific desensitization by repeated exposures.

Most authorities agree that experimental production of ordinary reactions to insects is difficult, but that in the average person, because of a long succession of exposures, the reactivity develops naturally and inevitably. Equally difficult, but probably possible is natural desensitization. During two years spent in a heavily mosquito-infested district of Florida I had as neighbor a native who slept nightly in a rough cabin with open windows devoid of glass or shutters. Although mosquitoes were as numerous and voracious as I have seen anywhere, he maintained that they never annoyed him. He had ample evidence of malaria but never bore any marks of bites.

Summary of Ordinary Effects of Insects.—1. Certain persons fail to react to the bite of a given insect.

2. The reaction of most people consists of an early wheal and a late papule.

3. The effect is probably due, not to the action of a secreted irritant, but to an acquired specific sensitization.

4. The specificity probably concerns the species or, at most, the order of insects.

5. Persons become sensitive to a particular species of insect in varying degrees.

6. Sensitization is difficult to induce in a nonsensitive person, and desensitization of a sensitive person is even more difficult and is also transient.

7. Passive transfer is possible but difficult and applies to the early wheal but not to the papule.

STUDY OF MOSQUITO-SENSITIVE PATIENTS

In contrast to the ordinary effects of insects cited extensively in the foreign literature, my research during the past ten years concerned larger and more violent effects. Instead of the small wheal and later small papule, the highly sensitive patient invariably displayed an early wheal several centimeters in diameter and a larger and much more significant twenty-four to forty-eight hour reaction, which was hot, red, swollen and painful and usually persisted for several days. General symptoms such as cough and prostration were common effects. These violent reactions, like the lesser ones cited, were found to be specific. More important was the observation that repeated inoculations produced a prompt and progressive improvement in the violent late reactions.

My previous report [22] included 4 such cases:

CASE 1.—Mrs. F. A. K., more than 50 years of age, was tested extensively and was given a course of inoculations of extracts of various species of mosquitoes, as described in detail in that report. She experienced a relative but incomplete reduction of her response to bites of the insects, yet the result was far from convincing. Unfortunately, death from carcinoma of the lungs supervened the following year.

This first unfavorable experience did not discourage a continuation of the study. It is gratifying to be able to state that 5 subsequent cases had an entired successful outcome.

CASE 2.—Mrs. V. R. H., aged 33, in addition to being sensitive to pollens, complained that mosquito bites produced large and persistent local swelling, even to the extent of swelling the eyes nearly shut. Her testing and treatment consisted of only two intracutaneous inoculations of small amounts of mosquito extracts on a single occasion. The result was entirely beyond expectation. Large local infiltrations occurred, and she had no unfavorable effects of bites in the succeeding seven years.

This amazing experience aroused the hope that it might be possible to desensitize persons to mosquitoes by a minimal number of injections.

CASE 3.—Mrs. H. J. B., aged 45, sensitive to certain foods and highly so to bites of mosquitoes, gave large persistent reactions to extracts of the insect. She received two series of a few inoculations each of such extracts in successive years, and in the five years following her first course experienced only the ordinary discomfort from repeated bites.

CASE 4.—Mrs. D. F., a nurse aged 40, had probably the most extreme reaction encountered. A detailed account of this patient's complaint will perhaps furnish the best clinical picture that can be given of extreme allergy to the bite of the mosquito. She had been sensitive to adhesive plaster for years, but far more important was her violent reactivity to the bites of mosquitoes extending back over a period of twenty years. The sites of the punctures always swelled excessively, sometimes resulting in red streaks which extended up the arm or the leg.

She was confined to the hospital at various times by such reactions. The erythema was often several inches in diameter and lasted from two days to a week. In 1917, while in the military service in France, she suffered a sting on the left cheek, and within a few hours there developed an infiltration so extensive that it almost closed the left eye. The lip also became so swollen that it was necessary for three days to feed her with a tube. During the succeeding years she experienced similar effects from attacks of mosquitoes up to the time when she consulted me in 1935. She received a course of specific treatment in the summer of 1935 and manifested improvement almost from the beginning. After the first four injections of the antigen I personally observed two mosquito bites, one on the wrist and the other on the ankle, which caused no reaction beyond the ordinary small wheal. Her freedom from severe reactions continued. Two years later she received a second course of inoculations and has had no trouble in the four years since treatment began.

Diagnosis has been made of the condition of 2 additional patients, and they have had a limited number of inoculations. Several others have been tested, but they need not be discussed in detail here, as their course conformed in all respects to that of the patients already mentioned. All patients treated except the first have had successful results.

The method of preparing the antigens from pure strains of the mosquitoes Aedes vexans, Aedes aldrichii and Culicella incidens, hatched in the laboratory, appeared in detail in the earlier report. I segregated the males and females for separate study and in some instances classified them according to age into mature, newly hatched and pupal. Antigens of each were of two types: (*a*) simple extracts in Coca's solution and (*b*) precipitates thrown down from fluid extracts of the insects with cold alcohol or a saturated solution of ammonium sulfate. The latter type of concentration, with later dilutions of varying strength, gave better reactions than the simple filtrates, but in other respects the two types of antigen acted similarly.

The early wheal always appeared within fifteen minutes and was entirely like that produced by extracts of bees (fig. 4). This usually faded in a short time but was succeeded in a few hours by a raised area of erythema, which continued to increase in size until in twenty-four hours it formed a hot, red, somewhat raised and painful infiltration usually 2 inches (5 cm.) or more in diameter and lasting for several days (fig. 3). Sometimes it occupied nearly the whole forearm or upper arm. The reactions in the various patients were mostly of this type except that in some instances vesicles appeared in the center of the infiltration. Such lesions can be seen in figures 4 and 6 of the earlier study.

Observations of these unusual large infiltrations are scanty in the literature. Kemper [23] described medium-sized wheals arising from three bedbug bites on the forearm and followed in eight hours by extensive hot erythema which in fifteen hours involved the whole forearm, the lower half of the upper arm and the back of the hand. Hecht [24] reported

a similar occurrence due to the sting of Anopheles maculipennis. Brown and his co-workers [30] reported an instance of Arthus' phenomenon with mosquito bites. Only a few isolated citations of these major effects have come to my attention, and they without evidence of specific treatment of the severe late reaction.

There appeared to be no doubt that the extreme effects of mosquitoes observed in my six patients were correctly ascribed to the bites. On repeated occasions the patient's arm, subjected to the sting of confined mosquitoes which had been hatched in the laboratory, exhibited typical immediate and delayed reactions of great severity, while several normal controls under the same conditions showed no unusual effects. The hatching of the mosquitoes in the laboratory and the subsequent vegetable diet for the insects assured that none of those used for experiment had partaken of blood.

Several important deductions resulted from this study. The three species of mosquitoes caused about equal reactions on a given patient. This fact seemed to indicate a specificity for the suborder but not for the species. The comparison of these effects with those of biting flies would be desirable, since these insects, like the mosquitoes, belong to the order Diptera.

Sex appeared not to be a factor in the antigenicity of the insects. The vegetarian male when injected into the skin caused a reaction as strong as that of the blood-sucking female. In this connection Hecht [31] reported on the separate antigenic properties of different parts of the mosquito. He made emulsions of the salivary glands, muscles, ovaries and other portions of the mosquitoes' bodies. Each of these injected intracutaneously into the skin of reactive persons produced effects similar to those of the insect's bite. These results, which were corroborated by other workers, convinced Hecht that the reacting substance of the salivary gland was likewise present in other tissues of the insect. The similarity of reactions to extracts of the male and female, together with the studies of Hecht, forced me to the conclusion that sensitization to the mosquito was not due to any poison in the venom, but to an antigen present in all parts of the mosquito, regardless of sex. It appeared likely that the injection of salivary secretion by mosquitoes in the act of feeding caused the extreme effects in these highly reactive patients because the fluid contained, in some degree, substances common to all parts of the insects' bodies.

The reaction to extracts of newly hatched mosquitoes was similar to that obtained when older insects were used. The pupae, on the other hand, failed to incite a reaction in a sensitive patient. This differs with

30. Brown, A.; Griffitts, T. H. D.; Erwin S., and Dyrenforth, L. Y.: Arthus's Phenomenon from Mosquito Bites, South. M. J. **31**:590, 1938.

31. Hecht, O.: Ueber Insektenstiche, Dermat. Wchnschr. **88**:793 and 839, 1929.

Kemper's observation for bedbugs. He stated that the youngest larvae of that insect caused as strong reactions as the mature insects.

A second inoculation of antigen in a former inoculation site gave rise to an undiminished early wheal, but in most instances it failed to elicit the former large twenty-four hour infiltration. The late reaction usually failed entirely to appear after the reinoculation. Extracts of one species of mosquito inoculated into a site previously inoculated with an extract of another species abolished the reactivity equally well. These findings indicated that it was easy to desensitize as far as the late reaction was concerned and also that the specificity applied to the whole suborder of mosquitoes rather than to the species. The ease with which local desensitization was attained was the main factor which encouraged me in the hope that the same result might, by repeated inoculations in ascending doses, produce the same action in a general sense. That this hope was justified is proved by the adequate clinical relief that followed specific treatment in several cases.

The antigen was found to be soluble in water and saline solution, insoluble in alcohol, nondialyzable, thermostable and specific. Numerous controls failed to react. These qualities, together with its occurrence in both sexes and Hecht's demonstration of its distribution in various portions of the mosquito's body, pointed to a heat-resistant, protein-bound antigen of this insect's body as the active principle in sensitization.

SUMMARY

Instances of extreme sensitization to the sting of the honeybee and the bite of the mosquito are described. With each species the immediate wheal was of considerable size, but the important reaction reached its height in twenty-four to forty-eight hours and consisted of a large, hot, red, painful, slightly raised infiltration which persisted for several days. With both species the reaction to the insect's puncture and to the intracutaneous inoculation of the extract was found to be due, not to the poison of the venom or to the salivary secretion, but to the body substance of the insect carried in this fluid. Extracts of the bodies of these insects contained antigens which were soluble in water, nondialyzable, thermostable and specific for the host in regard to the group rather than the species. These antigens had the property of causing large immediate wheals and later infiltrations similar to the effects produced by the insect's puncture of the skin. It was found possible, by reinoculation in the same site, to desensitize locally as far as the late reaction but not the immediate wheal was concerned.

Passive transfer by the Prausnitz-Küstner technic was demonstrated for the bee and imperfectly for the mosquito, but in each instance for the immediate reaction only. Repeated injections of antigens in increas-

ing doses resulted in several instances in adequate general desensitization to the violent effects of the punctures of each species of insect. This successful result led to the conclusion that these antigens are probably essentially different from those causing the ordinary mild reactions of the same insects.

The results reported here and in previous articles afford conclusive evidence that (1) extreme hypersensitiveness to the sting of the bee and other Hymenoptera, with its hazard to human life, can be eliminated, usually for a period of years, by a series of specific inoculations, and (2) large, painful and toxic infiltrations from bites of mosquitoes can be similarly prevented.

The Lederle Laboratories are now prepared to furnish both of these antigens for diagnosis and treatment.

404 Medical-Dental Building.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1939

STANLEY COBB, M.D.
BOSTON

ANATOMY OF THE REFLEXES

One of the important events of the year for clinical neurologists is the publication of Fulton's "Physiology of the Nervous System." [1] The book is more accurately described as a physiologic anatomy of the central nervous system, for several aspects of neurophysiology have been slighted or omitted but the coordinated exposition of anatomy and function is extraordinarily well done and is just the sort of information that the student of neurology needs before he undertakes clinical problems.

Chapter XV is written largely by Lorente de Nó and is especially significant because it brings together for the first time a group of observations that have changed the trend of neurologic thought in recent years. Formerly the reflex arc was considered the epitome of nervous action; combinations of reflex arcs were thought to be added together and organized into more and more complex action patterns, but this concept has been found to be too simple. Even in such rudimentary reflexes as the flexion of the leg there was found to be a prolongation of contraction, or after-discharge, that could not be explained on the basis of the simple reflex arc. As long ago as 1923 Forbes [2] clearly stated that this must be due to a "reverberation" effect set up in a complex network of neurons whenever a simple reflex arc is set off. Recently Lorente de Nó has studied this problem in great detail by investigations both in the field of microscopic anatomy and in that of experimental electrophysiology. His work is well summarized in three papers [3] dealing with the activity of the chains of internuncial neurons which complicate the simplest reflex arc. Much of his work was on the vestibular nuclei and tracts in the bulb. The experiments show how a single stimulus can set up a long-continued set of neural events which cause sustained reflex action. In fact, these internuncial neurons form the greater part of the nerve tissue, and many of the functions of the nerve center are explainable in terms of threshold changes caused by long-lasting bombardments of the nerve cell by internuncial pathways. Long

1. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938, p. 675.
2. Forbes, A.; Cobb, S., and Cattell, H.: Am. J. Physiol. **65**:30, 1923.
3. Lorente de Nó, R.: J. Neurophysiol. **1**:187, 195 and 207, 1938.

circuiting and reverberation explain the continuity of action of reflex mechanisms. Summation, inhibition, facilitation, after-discharge and reciprocal contractions of muscles are examples. It is not a mere matter of stimulus and response, which at best would give jerky and awkward motor results, but a matter of fine, continuous intergradations of stimuli, probably caused by changes in threshold and summation at the multitudinous synaptic knobs on the millions of nerve cells. The experiments not only explain cord and bulbar reflexes but have been applied to the cerebral cortex. The histologic work of Lorente de Nó [4] on the brains of young mammals has shown that the most important relations of cortical nerve cells are the vertical connections through axons, dendrites and collaterals. Here, at the highest level, one finds a beautiful apparatus of continuous, "reverberating" reflex action.

PSYCHOSOMATIC RELATIONS

In December 1938 the Association for Research in Nervous and Mental Disease held a two-day symposium on "The Inter-Relationship of Mind and Body." Early in 1939 appeared the first number of a new journal, *Psychosomatic Medicine*, sponsored by the Committee on Neurotic Behavior of the National Research Council. These two events show that a long period of educational development is reaching fruition. For twenty-five years Adolf Meyer has been urging the psychobiologic point of view, emphasizing that in medical practice the personal situation must be taken into account—not only the body and its internal environment but also the psychologic reactions and the external environment. A balance sheet should be made up of the patient's assets and liabilities before treatment is prescribed, and that treatment must be medical, social and psychologic.

This point of view has long been held by the masters in medicine; it is not new, but its recent emphasis and development are important. It enriches the science of medicine, and it gives meaning to the art. Not that somatic medicine is all science and psychologic medicine all art—far from it! But it brings these two together and points out problems and methods, besides trying to expound what is known. "It brings . . . to the study of disease an attack in which it is specifically recognized that every human being is a whole individual and not a loose combination of physical and psychic factors." [5] Note well that I do not say "the individual must be studied as a whole" or "the total situation must be considered." These dogmas say too much, and in so doing spoil themselves. It is plain common sense that the individual cannot be studied as a whole—one must begin somewhere, and as

4. Lorente de Nó, R., in Fulton,[1] chap. 15.

5. Psychosomatic Medicine, editorial, J. A. M. A. **113**:503 (Aug. 5) 1939.

soon as a beginning is made at one point the study of the whole is sacrificed. Studying the "whole individual" would have to be a sort of armchair contemplation that would lead nowhere. Likewise, no student ever completed a description of the "total situation" of another person—it cannot be done. What one can do is this: approach the study of disease recognizing that every human being is a whole individual and not the mere sum of his parts. That is something different, and only thus can one study the parts intelligently.

The new journal *Psychosomatic Medicine* has papers on diverse topics, but all deal primarily with phenomena which may be viewed from either the psychologic or the medical angle. Ingram's [6] review of the functions of the hypothalamus stresses the point that the variety of functions attributed to such a small structure makes the theories seem incredible. This part of the brain is an integrating mechanism for vegetative functions; it influences lower, subordinate neural mechanisms, and is influenced to a certain extent by cerebral control. There is good evidence that neurons in the hypothalamus are concerned with sleep, emotional expression, body temperature and the activities of the viscera. It is probable that these nuclei also have control over the metabolism of mineral substances, carbohydrates, fats and perhaps protein. In this field, however, more work must be done before proof is established. Much has been done in relation to water metabolism, but some facts are still confusing. The relation to the functions of reproduction are less well known. Localization of any one of these functions to any single hypothalamic nucleus is as yet impossible; in fact, it is probable that there is no localization of that sort. A bibliography of 399 titles shows what extensive work has been done in recent years on this group of cerebral nuclei.

Liddell and his co-workers [7] have produced in sheep a state that resembles certain neuroses in man. These sheep have a cardiac disorder disclosed by a rapid and irregular pulse brought on by stimuli which have no effect on normal animals. The neurosis is induced by a technic similar to that employed by Pavlov. The animals are "conditioned," i. e., taught to make discriminations between stimuli. When this process of discrimination is refined, when it is made difficult by delay or interruptions, the neurotic behavior develops. Cook [8] has developed "experimental neurosis" in white rats by first training and then confusing and frustrating them. The resulting behavior, as described in his paper and shown in his moving pictures, is certainly convincing

6. Ingram, W. R.: Psychosom. Med. **1**:48, 1939.

7. Anderson, O. D.; Parmenter, R., and Liddell, H. S.: Psychosom. Med. **1**: 93, 1939.

8. Cook, S. W.: Psychosom. Med. **1**:293, 1939.

proof that the animals are undergoing a severe psychologic disintegration especially affecting their motor performances by the appearance of such symptoms as tremors, spasms and fits.

Cardiovascular neuroses are treated in a review by Caughey [9] and in a symposium on hypertension. Solomon, Darrow and Blaurock [10] show beautiful continuous records of blood pressure and palmar sweat reactions during emotional stimulation. Hostility and perplexity caused large changes in blood pressure and small changes in palmar sweating. Passive patients showed large changes in both. The authors demonstrate by records, what has long been known clinically, that the autonomic system of man reacts selectively to various stimuli. Saul [11] describes 7 cases of essential hypertension in which psychoanalysis revealed chronic hostility and unsuccessful rebellion with inhibited heterosexuality as the main psychodynamic personality trait. Mittelmann and Wolff [12] made a coordinated study of emotional and physiologic phenomena; changes in temperature of the skin appeared to be an especially useful indicator. Induced emotional stress was shown to cause a marked drop in skin temperature, and if sustained, cold hands resulted for long periods. In patients with Raynaud's disease emotional stress would cause a fall in temperature and attacks of pain with cyanosis. The degree of discomfort was the resultant of the interplay between the factors of emotional stress and environmental temperature.

More specific psychosomatic relationships are discussed in special papers and case reports on anorexia nervosa,[13] neurodermatitis,[14] asthma [15] and ovarian activity.[16]

At the meeting of the Association for Research in Nervous and Mental Disease there was conspicuous variation in ideology and nomenclature; in fact, a number of the discussions were too vague to lead anywhere. Some good data were presented, however, in several fields. In a symposium on the alterations of mental and emotional proceses by chemical agents [17] there were discussions on oxygen, vitamin deficiency and the results of administration of barbiturates, bromides, benzedrine

9. Caughey, J.: Psychosom. Med. **1**:311, 1939.

10. Solomon, A. P.; Darrow, C. W., and Blaurock, M.: Psychosom. Med. **1**: 118, 1939.

11. Saul, L. J.: Psychosom. Med. **1**:153, 1939.

12. Mittelmann, B., and Wolff, H. G.: Psychosom. Med. **1**:271, 1939.

13. Rahman, L.; Richardson, H. B., and Ripley, H. S.: Psychosom. Med. **1**: 335, 1939.

14. Ackerman, N. W.: Psychosom. Med. **1**:366, 1939.

15. McDermott, N. T., and Cobb, S.: Psychosom. Med. **1**:203, 1939.

16. Benedek, T., and Rubenstein, B. B.: Psychosom. Med. **1**:245, 1939.

17. McFarland, R. A.: A. Research Nerv. & Ment. Dis., Proc. **19**:112, 1939. Jolliffe, N.: ibid. **19**:144, 1939. Curran, F. J.: ibid. **19**:154, 1939. Bloomberg, W.: ibid. **19**:172, 1939. Bromberg, W.: ibid. **19**:180, 1939.

and marihuana. The physiologic mechanisms operative in the production of emotional behavior were discussed by Bard [18] and Fulton.[19] The physiologic changes caused by emotions were considered by another group of speakers: Whitehorn [20] showed that the heart rate, well known to be increased by emotional stimulation in normal and in neurotic persons, might show no change at all in psychotic patients. Likewise, respiration is a good indicator of the emotional content of the patient's thoughts. Asthma was discussed by Deutsch [21] as one of the best examples of the psychogenesis of a medical symptom.

One of the discouraging things about the meeting was the loose way in which trained men used such terms as "physical," "mental," "organic" and "functional." In difficult discussions in which clarity of meaning was important, the sense was usually obscured by the use of ambiguous terms.

I feel that it is imperative for workers in this field to give up undefinable terms and use simple medical language understood by all physicians, e. g., "psychologic," "neurologic," "medical" and "surgical." For example, in using the terms "medical" and "psychologic" one realizes that they have no biologic significance. What is considered psychologic today may be medical tomorrow, and vice versa. They represent, however, useful administrative divisions of a hospital or university.

When a patient with hemiplegia comes to the hospital he is sent to the neurologic ward; a woman in labor goes to the obstetric pavilion; a patient with prostration and fever is sent to the medical ward, and a moody, depressed man, to the psychiatric ward. Obviously, the nurse in the admitting office and the intern in the emergency ward know that "medical," "obstetric" and "psychiatric" are words that have a practical and fairly definite significance in that particular hospital: They signify what service and which physician will care for the patient. It would be better if the idea never entered the thoughts of the doctor or nurse that one set of symptoms was "physical" and another "mental," one "organic" and the other "functional." Unfortunately, this idea often arises in the worst way; too often the physician's attitude is that patients with "mental" or "functional" disturbances have "nothing wrong"; but it is obvious that there *is* "something wrong" when a patient has symptoms of any kind. The physician merely expresses that the situation is too complex for his diagnostic instruments or too subtle for his mental caliber when he tells a patient that "there is nothing the matter" or "it's all imagination." Moreover the patient usually recognizes the physician's limitations and goes away to look up another doctor, or often a quack.

18. Bard, P.: A. Research Nerv. & Ment. Dis., Proc. **19**:190, 1939.
19. Fulton, J. F.: A. Research Nerv. & Ment. Dis., Proc. **19**:219, 1939.
20. Whitehorn, J. C.: A. Research Nerv. & Ment. Dis., Proc. **19**:256, 1939.
21. Deutsch, F.: A. Research Nerv. & Ment. Dis., Proc. **19**:271, 1939.

The source of this curious medical attitude lies perhaps in the training that medical students receive. Brought up in the pathologic tradition of Virchow, taught that symptoms are caused by "lesions," they come to believe that if they can see no lesion (macroscopically or microscopically) the symptoms presented must have been due to some mythical process known as a "functional" state. But it never seems to occur to them that a function must be a function of some structure, unless they invoke structureless supernatural agencies.

Thus it is apparent that the dichotomies "mental" and "physical," "functional" and organic" are inexact and misleading distinctions. In a loose way they signify degrees of complexity; but that is all. The knee jerk is called a "physical" reaction, but the more complex reactions of the nervous system, such as memory, are called "mental." This is an illogical procedure, unless it is realized that there is a perfectly continuous series of more and more highly integrated responses between those two functions of the nerve tissue, and that the line between "physical" and "mental" is entirely arbitrary and meaningless. Psychologic phenomena such as thinking, wishing and dreaming are just as much functions of the organism as are breathing, running and digesting. They are merely more complex and less understood. Unless supernatural phenomena are accepted there can be no functions of man other than "organic" functions. It is important not to let mythologic values creep into one's thinking, as apparently one does when one speaks of "the interrelationship of mind and body."

Terms that have no definite connotation have no place in scientific discussion. I therefore recommend that the useless and misleading terms "physical" and "mental," "organic" and "functional," and "somatic" and "psychic" be dropped, and that in their place definable and acceptable terms be used. I submit that such terms as "medical," neurologic," "psychiatric," "psychologic" and "anatomic" have useful meanings to most people; they tell to what department or to what professor the problem should be taken; they have no biologic significance; they are entirely practical and administrative. Thus, by defining terms and omitting ambiguous words one clarifies this age-old subject of "psyche and soma." One must put aside superstition, mythology, parallelism and other outworn creeds, and accept simply the fact that all stimuli which play on an organism are physical, that all phenomena which take place in the organism are organic and that the psychologic processes, although the most complex, are not exceptions.

THERAPY

For many years treatment of nervous and mental disorders seemed to be making little headway. Medical men were discouraged and progress seemed to be only along psychologic lines. The great contribution of

Freud (whose death is reported just as this review is being written) has been already discussed in these pages.[22] It will be years before his theories can be evaluated. Many of his inspired intuitions are doubtless correct, but they cannot be looked on as facts until more data have accumulated and until they have been tested by other methods. Murray [23] has made a start in this direction. In his book on the study of personality he shows how many methods of psychologic testing have been brought to bear on freudian postulates. In general the results suggest that the postulates are valid. Such investigation is greatly needed because wholehearted acceptance of a "school of thought," even if started and developed by a great man like Freud, never leads to anything but wordy controversy. Whichever of the theories turn out later to be correct and which erroneous, one can be confident that some of them are correct because one knows of many patients with psychoneurosis who are relieved by psychoanalysis—and "the proof of the pudding is in the eating." One also knows of failures, and these are often widely known because the patients go on to practitioners of other types. Nevertheless, Freud in his last years saw his method accepted as an important implement of psychotherapy and knew that his theories had profoundly affected social thinking and artistic production.

During the last two years new forms of medical treatment for nervous disorders have appeared. The doldrums in which medical therapy stagnated while psychotherapy pressed ahead have suddenly been dissipated, first by the radical shock therapies and surgical procedures [24] and now by sound progress in chemistry and physiology.

The growing understanding of vitamin deficiency has led to remarkable improvement in the treatment of the psychoses, not only those associated with specific syndromes, such as pellagra,[25] but alcoholic psychoses, both acute and chronic,[26] and psychoses of old people with failure of attention and memory.[27] Here especially nicotinic acid appears to do wonders, when the physician might be too ready to make a diagnosis of senility and arteriosclerosis. The role of thiamin in the neuritic

22. Cobb, S.: Review of Neuropsychiatry for 1935, Arch. Int. Med. **56**:1287 (Dec.) 1935; Review of Neuropsychiatry for 1936, ibid. **58**:1111 (Dec.) 1936.

23. Murray, H. A.: Explorations in Personality, New York, Oxford University Press, 1938.

24. Cobb, S.: Review of Neuropsychiatry for 1937, Arch. Int. Med. **60**:1098 (Dec.) 1937.

25. Williams, R. R., and Spies, T. D.: Vitamin B_1 and Its Use in Medicine, New York, The Macmillan Company, 1939.

26. Wexberg, E.: Am. J. Psychiat. **95**:1127, 1939.

27. Cleckley, H. M.; Sydenstricker, V. P., and Geeslin, L. E.: Nicotinic Acid in Treatment of Atypical Psychotic States Associated with Malnutrition, J. A. M. A. **112**:2107 (May 27) 1939.

aspect of these illnesses is of equal importance. Old persons with muscular weakness and atrophy may well be in that vicious circle of poor appetite–asthenia–less appetite, due not to circulatory disturbances and senility but to easily curable vitamin deficiency. Nevertheless, careful differential diagnosis is necessary, for only those neurologic disorders specifically caused by vitamin lack will be helped by vitamin therapy and many useless treatments have been given in cases of multiple sclerosis, muscular atrophy and dystrophy, paralysis agitans and cerebral arteriosclerosis.

Epilepsy has continued as a point of active research. Merritt and Putnam [28] deserve a great deal of credit for developing a new drug, sodium diphenyl hydantoinate,[29] which inhibits convulsions in many cases without causing a feeling of sleepiness or depression. Moreover, it is effective in some cases in which phenobarbital and bromides have not worked well. For certain patients the most efficacious treatment has been a combination of sodium diphenyl hydantoinate (½ grain [0.03 Gm.] after each meal) and phenobarbital (1½ grains [0.1 Gm.]) at night. The dose is, of course, determined only after trial with each patient.

Benzedrine sulfate has now been used for several years and has been tried in the treatment of many diseases.[30] In cases of narcolepsy it has proved to be a valuable remedy,[31] but there are dangers in excessive dosage. It has been of benefit in many cases of paralysis agitans, especially in those with inertia, slowness and more rigidity than tremor. It is best used in conjunction with one of the atropine series. Because of the enlivening effect which the drug has on most normal persons, it was expected that it would be of use in the treatment of both neurotic and psychotic depressions. Unfortunately, the results of treating such conditions with benzedrine have been disappointing. The patients have become somewhat more active, as a rule, but their restlessness has often given rise to an agitation worse than the depression. Davidoff and Reifenstein [32] have found that catatonic schizophrenia can sometimes be improved by large daily doses. Some patients with mildly depressed mood and lack of energy have been benefited. Especially interesting in this regard is Bloomberg's [33] experience in the treatment of alcoholism.

28. Merritt, H. H., and Putnam, T. J.: Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders, J. A. M. A. **111**:1068 (Sept. 17) 1938.

29. Put on the market by Parke, Davis & Co. as "dilantin."

30. Reifenstein, E. C., Jr., and Davidoff, E.: New York State J. Med. **39**:42, 1939.

31. Prinzmetal, M., and Bloomberg, W.: Use of Benzedrine for Treatment of Narcolepsy, J. A. M. A. **105**:2051 (Dec. 21) 1935.

32. Davidoff, E., and Reifenstein, E. C.: Psychiatric Quart. **13**:127, 1939.

33. Bloomberg, W.: New England J. Med. **220**:129. 1939.

He gave benzedrine sulfate to 21 alcoholic patients in doses of 10 mg., in the morning and at noon, with rarely a third dose in the evening; 14 of these patients found that the "lift" given them by the drug made it easier to keep away from alcohol, and 6 of them abstained from its use for six months. It seems probable that one type of alcoholic persons can be distinctly helped in this way. The dangers of insomnia, hypertension and habit formation must be guarded against.

Potassium has been found to give relief from Ménière's disease. This most incapacitating form of vertigo occurs in a definite setting. There are sudden attacks of dizziness with tinnitus, followed by nausea, vomiting and even unconsciousness. The disease occurs with progressive deafness, but little is known of the pathologic picture.[34] Formerly the chief method of medication was sedative. In 1934 Furstenberg and his associates[35] recommended ammonium chloride and a saltless diet. This met with success in some cases, but was difficult to carry out for most patients. Now Talbott, Brown, Coombs and Consolazio[36] have shown that the pathogenesis of Ménière's disease is not related to hydration, alkalosis or high sodium intake. The symptoms can frequently be relieved by the simple administration of potassium chloride in 25 per cent solution, about 6 Gm. per day. For stubborn cases surgical division of the vestibular nerve is necessary. Injection of alcohol is to be avoided.

In the field of myopathy headway is at last being made. The use of prostigmine for myasthenia gravis, both hypodermically and by mouth, has proved to be effective.[37] Many patients who would have been helpless or dead are now leading fairly active lives owing to this drug, but it must be administered six or eight times a day.

Myotonia congenita is a rare disorder in which muscular contraction leads to contracture and the patient is unable to relax in time to make the next necessary movement. As a symptom it occurs in syndromes such as dystrophia myotonica. Kennedy and Wolf[38] have shown that the muscular spasm of "myotonia" may be relieved by quinine. Another rare disease, also inherited, is familial periodic paralysis. Here the

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34. Cairns, H., and Hallpike, C. S., in discussion on Ménière's Syndrome, Lancet **1**:1163 and 1171, 1938.

35. Furstenberg, A. C.; Lashmet, F. H., and Lathrop, F.: Ann. Otol., Rhin. & Laryng. **43**:1035, 1934.

36. Talbott, J. H.; Brown, M. R,; Coombs, F. S., and Consolazio, W. V.: Proc. Soc. Exper. Biol. & Med. **38**:421, 1938.

37. Viets, H. R.; Mitchell, R. S., and Schwab, R. S.: Oral Administration of Prostigmine in Treatment of Myasthenia Gravis, J. A. M. A. **109**:1956 (Dec. 11) 1937.

38. Kennedy, F., and Wolf, A.: Quinine in Myotonia and Prostigmine in Myasthenia: Clinical Evaluation, J. A. M. A. **110**:198 (Jan. 15) 1938.

patient gradually goes into flaccid quadriplegia, which may last for hours. Several workers [39] have found that the administration of potassium chloride immediately cures the paralysis.

THE MYOPATHIES

The investigations that have led to these improvements in the therapy of the myopathies have also given to the physiologist data of fundamental importance concerning the function of muscle, and to the clinician facts that help in the classification of muscle disease. Myasthenia gravis is made worse by quinine and relieved by prostigmine and potassium. Myotonia congenita is aggravated by prostigmine and relieved by quinine [40] and calcium. The very antagonism of these two muscular disorders points to a relationship. Family periodic paralysis is relieved by potassium, and attacks may be brought on by ingestion of dextrose. The details of these metabolic interrelationships are yet to be worked out. In general, they indicate that the disorder lies in the muscle, not in the nervous system, if the myoneural junction is considered part of the muscle. The pathologic extremes of muscular contraction seen in these diseases are contracture, on the one hand, and paralysis, on the other. Bremer [41] considers that the premature, undeveloped muscle may have a pathologic susceptibility to contracture. This may be the phenomenon of "myotonia" seen as part of the syndrome of some muscular dystrophies, especially the type known as dystrophia myotonica. When the symptom appears alone it is called Thomsen's disease or myotonia congenita. At the other end of the line is family periodic paralysis, related by such intermediate syndromes as myasthenia gravis, progressive muscular dystrophy, myotonia congenita and dystrophia myotonica. These form one closely allied group of muscular disorders, the familial myopathic group. The familial myelopathic group is entirely different, having lesions of the cord and secondary atrophies.

SCHIZOPHRENIA AND MANIC-DEPRESSIVE PSYCHOSIS

Kraepelin's sharp differentiation between these two types of psychosis has long been viewed with skepticism by leading psychiatrists. It is apparent that the extreme conditions (the typical or "textbook" syndromes) are quite distinct: In schizophrenia the difficulty is with the

39. Herrington, M. S.: Successful Treatment of Two Cases of Familial Periodic Paralysis with Potassium Citrate, J. A. M. A. **108**:1339 (April 17) 1937. Pudenz, R. H.; McIntosh, J. F., and McEachern, D.: Role of Potassium in Familial Periodic Paralysis, ibid. **111**:2253 (Dec. 17) 1938. Gammon, G. D.: Proc. Soc. Exper. Biol. & Med. **38**:922, 1938.

40. Kolb, L. C.; Harvey, A. M., and Whitehill, M. R.: Bull. Johns Hopkins Hosp. **62**:188, 1938.

41. Bremer, F.: J. Physiol. **76**:65, 1932.

content of thought; there are fixation on topics and false systematization of ideas. In contrast to this, the manic-depressive psychoses are essentially disorders in mood which dominate the personality and may cause long periods of depression or elation. Moreover, there is striking evidence that schizophrenia is inherited as a recessive character,[42] while the manic-depressive personality seems to act more like a dominant character in its inheritance. For example, Slater [43] found that the parents and children of manic-depressive patients have sixty times as great a likelihood of being affected as have similarly studied normal controls (19.7 per cent in families of patients, as compared with 0.3 per cent in a control group). Such are the distinctions between the typical psychoses. Nevertheless, it is becoming more evident that the two syndromes overlap and that the one merges into the other. In fact, most cases cannot be clearly classified because there is disturbance both of mood and of topical thought, and even the conspicuously schizophrenic reactions, such as catatonia, may be cyclic and swing from stupor to excitement.

Such clinical observations have long made investigators speculate as to some chemical cause for these psychoses, some metabolic variation that would explain the changing mental state. The great difficulties involved in careful metabolic studies of uncooperative patients have, however, prevented progress and vitiated many observations. Gjessing [44] deserves great credit for having patiently and slowly met all obstacles to metabolic research on psychotic patients; during the last ten years he has made carefully controlled observations on a group of patients with periodic psychoses of the catatonic type. On some patients repeated analyses of the blood and urine and determinations of oxygen consumption have been made over periods of years, with hundreds of observations on each patient. The results are published in three important papers.[45] The main conclusion is that there exists one type of cyclic psychosis in which the mental changes run parallel with a periodic variation in nitrogen balance. Retention is observed during the more normal period, with a peak at the onset of stupor; then overexcretion begins, and the mental symptoms disappear in a few days. The basal metabolic rate is lower during the period of retention and higher during the period of overexcretion. Many other laboratory and clinical observations were made, but these are the most significant. Of perhaps more practical importance is Gjessing's discovery that thyroid medication will

42. Kallmann, F. J., and Rypins, S. J.: The Genetics of Schizophrenia, New York, J. J. Augustin, Publisher, 1938.

43. Slater, E.: Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:1, 1938.

44. Gjessing, R.: J. Ment. Sc. **84**:608, 1938.

45. Gjessing, R.: Arch. f. Psychiat. **96**:319, 1932; **104**:355, 1935; **109**:525, 1939.

greatly improve some of these patients; the nitrogen retention is prevented and the cyclic psychosis disappears. He emphasizes the fact that in most psychiatric patients this relationship of *Pathophysiologie* to mental symptoms is not found, that he is describing a small group. Nevertheless, the important fact is that many good psychiatrists have for years believed that the cyclic psychosis had an origin based on metabolic dysfunction, and now Gjessing has brought evidence indicating that this is true in recurrent catatonic stupor. Even though he gives many cases in which the results are confusing, that means only that the methods are as yet too crude to determine the exact mechanisms.

The "shock treatment" of psychoses goes on with somewhat diminished enthusiasm. A critical survey of the results is well nigh impossible because of the difference in terminology used by the members of different hospital staffs and the different standards of "improvement" and "remission." Nevertheless, it is apparent that the original claims of "80 per cent remission" were statistically unsound. The better controlled results in this country indicate that the shock treatment in cases of early schizophrenia causes remissions sooner than could be expected with general hospital care, but that these remissions occur with no greater frequency than when good, individual psychiatric therapy of the conservative type is used.[46] In patients with chronic disease the shock treatment often improves the mental status so that they can be moved from a ward for disturbed patients to a better environment, but rarely is there a remission that allows the patient to return home, and gradual reversion to the former state is the rule. A "total push" with extra nursing, occupation and exercise [47] has been shown to accomplish as good results as the convulsive therapies. One feels doubtful of the ethical standards that allow "shock treatment" to be given for the purpose of making nursing easier for the hospital administration. It comes dangerously close to punishment, and logically one might ask: "Why not euthanasia?" It is devoutly to be wished that the crude empiric methods of shock and convulsion will soon be replaced by scientifically controlled procedures that are known to do no harm to the brain.

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46. Gelperin, J.: Spontaneous Remissions in Schizophrenia (Cincinnati General Hospital, 1933-1937), J. A. M. A. **112**:2393 (June 10) 1939. Guttmann, E., and Mayer-Gross, W.: J. Neurol. & Psychiat. **2**:25, 1939.

47. Myerson, A.: Am. J. Psychiat. **95**:1197, 1939. Tillotson, K. J.: ibid. **95**: 1205, 1939.

Book Reviews

Physical Diagnosis. By Richard C. Cabot and F. Dennette Adams. Twelfth edition. Price, $5. Pp. 846, with 391 illustrations. Baltimore: William Wood & Company, 1938.

The reviewer, who learned physical diagnosis from the fourth edition, is amazed to note the increase in size of the book in the present (twelfth) edition. One wonders what there is to add to a subject such as physical diagnosis. Yet in looking over the present volume one has no feeling of anything superfluous. Cabot still undoubtedly holds his own in the forefront of authors of texts on physical diagnosis. Here and there one might comment on a small point—for example, on page 99 under the subject of the breath it is noted that a "mousey" breath indicates pronounced hepatic failure. This is presented apparently as a new observation, although the characteristic odor of the breath in cirrhosis was described many years ago by Umber as "fetor hepaticus" and is certainly no novelty.

Handbook of Histological and Cytological Technique. By R. R. and S. H. Bensley. Price, $2. Pp. 167. Chicago: University of Chicago Press, 1938.

Bensley and Bensley have prepared a comprehensive manual of laboratory methods for the histologic worker which should prove valuable.

In the section on technics for the study of fresh tissues the authors discuss supravital stains, microdissection, tissue transplants into the anterior chamber of the eye and the Altmann-Gersh freezing-drying method.

They present not only all the older standard technics for the preparation and staining of fixed tissues but more recently introduced methods, such as the use of dioxane (diethylene dioxide) in dehydration. The book includes a section on the care of the microtome, sharpening of the knife and maintenance of laboratory equipment. A copy of this handbook should be in every histologic laboratory.

The Proceedings of the Charaka Club. Volume IX. Price, $5. Pp. 204, with illustrations. New York: Richard R. Smith, 1938.

The reviewer has looked with pleasure through the delightful volume of transactions of the Charaka Club. It seems a pity that the proceedings of an intimate group, meeting not only on scientific but on social grounds, should be thrown open to the public by placing the book on the general market. Members speak in serious or in lighter vein, and while many of the articles represent original investigation of medical-historical subjects, others are obviously occasional pieces or at least discourses intended for an intimate group. Ordinarily material of this sort is held as a rather closely guarded treasure for the members of whatever club or society is in question.

Studies on the Size of the Red Blood Cells, Especially in Some Anemias. By Erik Mogensen. Pp. 216, with 32 figures and 29 tables. Copenhagen: Ejnar Munksgaard; London: Oxford University Press, 1938.

Dr. Mogensen's handsome monograph on the size of the red blood cells seems to include all there is to be known on this subject. There are chapters on methods of determining the size of the red cells, followed by the author's measurements for normal persons and finally detailed discussions of the size of the cells in various diseases. There are many interesting tables and curves as well as a bibliography of 302 references. The book should be of great use to the hematologist and the special student.

Archives des maladies professionnelles, hygiene et toxicologie industrielles. Vol. 1, No. 1, 1938.

This new publication is devoted to occupational disease, the increasing importance of problems related to health in industry having prompted its appearance. The management proposes to publish every two months original manuscripts, résumés and abstracts of the French and foreign literature and reports on current events (legislation, work of institutes and compensation laws). This eighty page journal should be of value to those interested in this phase of medicine.

Clinical Biochemistry. By Abraham Cantarow and Max Trumper. Second edition, revised. Price, $6. Pp. 66, with 11 tables and 15 figures. Philadelphia: W. B. Saunders Company, 1939.

This book deals briefly and somewhat diagrammatically with clinical biochemistry from the point of view of the practicing physician. There is a great deal of useful information which gives one a quick orientation on biochemical matters. Here and there one feels the lack of discussion of fundamentals, but further discussion would doubtless increase the size of the book unduly. The reviewer is inclined to criticize the chapter on gastric function, which is inadequate and deals with the subject from an out of date point of view. On the whole, the book should be helpful to the busy practitioner.

News and Comment

Award of Certificate of Merit.—Dr. William Washington Graves, professor of neuropsychiatry, St. Louis University School of Medicine, was awarded a certificate of merit and a gold medal for scientific accomplishment for his classification of scapulas and other inherited characters and for his discovery of the age incidence principle of investigation, at a meeting of the St. Louis Medical Society held in his honor on Oct. 24, 1939. This is only the third occasion on which the St. Louis Medical Society has given this certificate of merit for scientific accomplishment. The award was first given to Dr. Evarts A. Graham and his associates Drs. Glover H. Copher, Warren H. Cole and Sherwood Moore, on June 7, 1927, for their work on cholecystography, and next to Dr. Edward A. Doisy, on March 19, 1935, for his achievements in hormone chemistry and physiology.

Notices

CUMULATED INDEX OF THE ARCHIVES OF INTERNAL MEDICINE

Requests have been received for a twenty year index of the ARCHIVES OF INTERNAL MEDICINE. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed $5 a copy. It will be appreciated if those who are interested in such an index will fill out and send the form which appears below to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

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Yellow fever, 403

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